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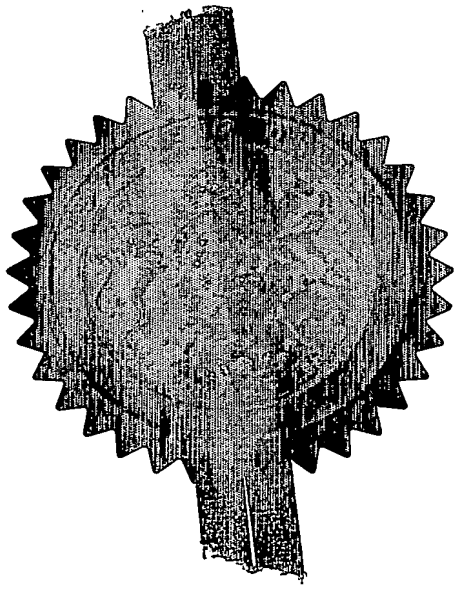

Signed Stephen Handley

Dated 22 October 2003

Patents Form 1/77

Patents Act 1977
(Rule)

07MAY03 E805422-1 D02934
P01/7700 0.00-0310446.0

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your reference 100863-2

2. Patent application number
(The Patent Office will fill in this part) 0310446.0

0 7 MAY 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 78224480003

If the applicant is a corporate body, give the country/state of its incorporation Sweden

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)* Lucy Padget

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4TG

Patents ADP number *(if you know it)* 78224 71002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	78
Claim *(s)*	3
Abstract	1
Drawing *(s)*	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Date 06/05/03

Jennifer Bennett, Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom: Shirley Douglas - 01625 510057

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Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.*

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c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

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CHEMICAL COMPOUNDS

This invention relates to chemical compounds, or pharmaceutically acceptable salts thereof. These compounds possess human 11-β-hydroxysteroid dehydrogenase type 1 enzyme (11βHSD1) inhibitory activity and accordingly have value in the treatment of disease states including metabolic syndrome and are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said compounds, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit 11βHSD1in a warm-blooded animal, such as man.

Glucocorticoids (cortisol in man, corticosterone in rodents) are counter regulatory hormones i.e. they oppose the actions of insulin (Dallman MF, Strack AM, Akana SF et al. 1993; Front Neuroendocrinol 14, 303-347). They regulate the expression of hepatic enzymes involved in gluconeogenesis and increase substrate supply by releasing glycerol from adipose tissue (increased lipolysis) and amino acids from muscle (decreased protein synthesis and increased protein degradation). Glucocorticoids are also important in the differentiation of pre-adipocytes into mature adipocytes which are able to store triglycerides (Bujalska IJ et al. 1999; Endocrinology 140, 3188-3196). This may be critical in disease states where glucocorticoids induced by "stress" are associated with central obesity which itself is a strong risk factor for type 2 diabetes, hypertension and cardiovascular disease (Bjorntorp P & Rosmond R 2000; Int. J. Obesity 24, S80-S85)

It is now well established that glucocorticoid activity is controlled not simply by secretion of cortisol but also at the tissue level by intracellular interconversion of active cortisol and inactive cortisone by the 11-beta hydroxysteroid dehydrogenases, 11βHSD1 (which activates cortisone) and 11βHSD2 (which inactivates cortisol) (Sandeep TC & Walker BR 2001 Trends in Endocrinol & Metab. 12, 446-453). That this mechanism may be important in man was initially shown using carbenoxolone (an anti-ulcer drug which inhibits both 11βHSD1 and 2) treatment which (Walker BR et al. 1995; J. Clin. Endocrinol. Metab. 80, 3155-3159) leads to increased insulin sensitivity indicating that 11βHSD1 may well be regulating the effects of insulin by decreasing tissue levels of active glucocorticoids (Walker BR et al. 1995; J. Clin. Endocrinol. Metab. 80, 3155-3159).

Clinically, Cushing's syndrome is associated with cortisol excess which in turn is associated with glucose intolerance, central obesity (caused by stimulation of pre-adipocyte differentiation in this depot), dyslipidaemia and hypertension. Cushing's syndrome shows a

number of clear parallels with metabolic syndrome. Even though the metabolic syndrome is not generally associated with excess circulating cortisol levels (Jessop DS et al. 2001; J. Clin. Endocrinol. Metab. 86, 4109-4114) abnormally high 11βHSD1 activity within tissues would be expected to have the same effect. In obese men it was shown that despite having similar or lower plasma cortisol levels than lean controls, 11βHSD1 activity in subcutaneous fat was greatly enhanced (Rask E et al. 2001; J. Clin. Endocrinol. Metab. 1418-1421). Furthermore, the central fat, associated with the metabolic syndrome expresses much higher levels of 11βHSD1 activity than subcutaneous fat (Bujalska IJ et al. 1997; Lancet 349, 1210-1213). Thus there appears to be a link between glucocorticoids, 11βHSD1 and the metabolic syndrome.

11βHSD1 knock-out mice show attenuated glucocorticoid-induced activation of gluconeogenic enzymes in response to fasting and lower plasma glucose levels in response to stress or obesity (Kotelevtsev Y et al. 1997; Proc. Natl. Acad. Sci USA 94, 14924-14929) indicating the utility of inhibition of 11βHSD1 in lowering of plasma glucose and hepatic glucose output in type 2 diabetes. Furthermore, these mice express an anti-atherogenic lipoprotein profile, having low triglycerides, increased HDL cholesterol and increased apo-lipoprotein AI levels. (Morton NM et al. 2001; J. Biol. Chem. 276, 41293-41300). This phenotype is due to an increased hepatic expression of enzymes of fat catabolism and PPARα. Again this indicates the utility of 11βHSD1 inhibition in treatment of the dyslipidaemia of the metabolic syndrome.

The most convincing demonstration of a link between the metabolic syndrome and 11βHSD1 comes from recent studies of transgenic mice over-expressing 11βHSD1 (Masuzaki H et al. 2001; Science 294, 2166-2170). When expressed under the control of an adipose specific promoter, 11βHSD1 transgenic mice have high adipose levels of corticosterone, central obesity, insulin resistant diabetes, hyperlipidaemia and hyperphagia. Most importantly, the increased levels of 11βHSD1 activity in the fat of these mice are similar to those seen in obese subjects. Hepatic 11βHSD1 activity and plasma corticosterone levels were normal, however, hepatic portal vein levels of corticosterone were increased 3 fold and it is thought that this is the cause of the metabolic effects in liver.

Overall it is now clear that the complete metabolic syndrome can be mimicked in mice simply by overexpressing 11βHSD1 in fat alone at levels similar to those in obese man.

11βHSD1 tissue distribution is widespread and overlapping with that of the glucocorticoid receptor. Thus, 11βHSD1 inhibition could potentially oppose the effects of glucocorticoids in a number of physiological/pathological roles. 11βHSD1 is present in human skeletal muscle and glucocorticoid opposition to the anabolic effects of insulin on protein turnover and glucose metabolism are well documented (Whorwood CB et al. 2001; J. Clin. Endocrinol. Metab. 86, 2296-2308). Skeletal muscle must therefore be an important target for 11βHSD1 based therapy.

Glucocorticoids also decrease insulin secretion and this could exacerbate the effects of glucocorticoid induced insulin resistance. Pancreatic islets express 11βHSD1 and carbenoxolone can inhibit the effects of 11-dehydocorticosterone on insulin release (Davani B et al. 2000; J. Biol. Chem. 275, 34841-34844). Thus in treatment of diabetes 11βHSD1 inhibitors may not only act at the tissue level on insulin resistance but also increase insulin secretion itself.

Skeletal development and bone function is also regulated by glucocorticoid action. 11βHSD1 is present in human bone osteoclasts and osteoblasts and treatment of healthy volunteers with carbenoxolone showed a decrease in bone resorption markers with no change in bone formation markers (Cooper MS et al 2000; Bone 27, 375-381). Inhibition of 11βHSD1 activity in bone could be used as a protective mechanism in treatment of osteoporosis.

Glucocorticoids may also be involved in diseases of the eye such as glaucoma. 11βHSD1 has been shown to affect intraocular pressure in man and inhibition of 11βHSD1 may be expected to alleviate the increased intraocular pressure associated with glaucoma (Rauz S et al. 2001; Investigative Opthalmology & Visual Science 42, 2037-2042).

There appears to be a convincing link between 11βHSD1 and the metabolic syndrome both in rodents and in humans. Evidence suggests that a drug which specifically inhibits 11βHSD1 in type 2 obese diabetic patients will lower blood glucose by reducing hepatic gluconeogenesis, reduce central obesity, improve the atherogenic lipoprotein phenotype, lower blood pressure and reduce insulin resistance. Insulin effects in muscle will be enhanced and insulin secretion from the beta cells of the islet may also be increased.

Currently there are two main recognised definitions of metabolic syndrome.

1) The Adult Treatment Panel (ATP III 2001 JMA) definition of metabolic syndrome indicates that it is present if the patient has three or more of the following symptoms:

- Waist measuring at least 40 inches (102 cm) for men, 35 inches (88 cm) for women;

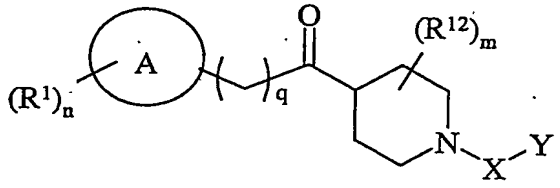
- Serum triglyceride levels of at least 150 mg/dl (1.69 mmol/l);
- HDL cholesterol levels of less than 40 mg/dl (1.04 mmol/l) in men, less than 50 mg/dl (1.29 mmol/l) in women;
- Blood pressure of at least 135/80 mm Hg; and / or
- Blood sugar (serum glucose) of at least 110 mg/dl (6.1 mmol/l).

2) The WHO consultation has recommended the following definition which does not imply causal relationships and is suggested as a working definition to be improved upon in due course:

- The patient has at least one of the following conditions: glucose intolerance, impaired glucose tolerance (IGT) or diabetes mellitus and/or insulin resistance; together with two or more of the following:
- Raised Arterial Pressure;
- Raised plasma triglycerides
- Central Obesity
- Microalbuminuria

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective 11βHSD1inhibitors, and accordingly have value in the treatment of disease states associated with metabolic syndrome.

Accordingly there is provided the use of a compound of formula **(I)**:



(I)

wherein:

Ring A is selected from carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^1 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl,

N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-5; wherein the values of R^1 may be the same or different;

X is a direct bond, -C(O)-, -S(O)$_2$-, -C(O)NR^{11}-, -C(S)NR^{11}-, -C(O)O- or -CH_2-; wherein $\mathbf{R^{11}}$ is selected from hydrogen and C_{1-4}alkyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

$\mathbf{R^3}$ and $\mathbf{R^6}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

$\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^7}$ and $\mathbf{R^9}$ are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

$\mathbf{R^8}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -$S(O)_a$-, -O-, -NR^{10}-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, -$OC(O)NR^{10}$- or -SO_2NR^{10}-; wherein **a** is 0 to 2; wherein $\mathbf{R^{10}}$ is selected from hydrogen and C_{1-4}alkyl;

$\mathbf{R^{12}}$ is methyl or ethyl;

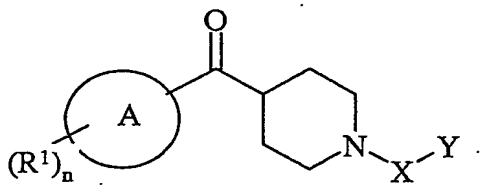
m is 0 or 1;

q is 0 or 1;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

In a further aspect of the invention, there is provided a compound of formula **(Ia)** wherein:



(Ia)

wherein:

Ring A is thienyl, furyl or thiazolyl;

$\mathbf{R^1}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl,

carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; or two R^1 on adjacent carbons may form an oxyC_{1-4}alkoxy group; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-3; wherein the values of R^1 may be the same or different;

X is -C(O)- or -$S(O)_2$-;

Y is C_{1-6}alkyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

R^3 and **R^6** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl and heterocyclyl; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

R^4, **R^5** and **R^7** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino,

acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is $-S(O)_a-$, $-O-$, $-NR^{10}-$, $-C(O)-$, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-OC(O)NR^{10}-$ or $-SO_2NR^{10}-$; wherein **a** is 0 to 2; wherein $\mathbf{R^{10}}$ is selected from hydrogen and C_{1-4}alkyl;

or a pharmaceutically acceptable salt thereof;

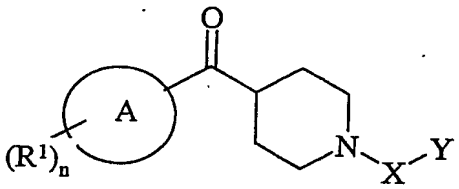
with the proviso that said compound is not

1-acetyl-4-[(4-methylthien-2-yl)carbonyl]piperidine;

1-acetyl-4-[(4-methyl-5-bromothien-2-yl)carbonyl]piperidine; or

1-benzoyl-4-[(5-methylthien-2-yl)carbonyl]piperidine.

In a further aspect of the invention, there is provided a compound of formula **(Ib)** wherein:



(Ib)

wherein:

Ring A is pyridinyl;

$\mathbf{R^1}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; or two R^1 on adjacent carbons may form an oxyC_{1-4}alkoxy group; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-3; wherein the values of R^1 may be the same or different;

X is $-C(O)-$ or $-S(O)_2-$;

Y is C_{1-6}alkyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

R^3 and R^6 are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl and heterocyclyl; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

R^4, R^5 and R^7 are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

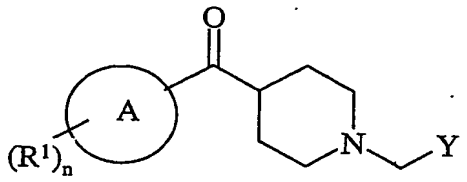
Z is $-S(O)_a-$, -O-, $-NR^{10}-$, -C(O)-, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-OC(O)NR^{10}-$ or $-SO_2NR^{10}-$; wherein **a** is 0 to 2; wherein $\mathbf{R^{10}}$ is selected from hydrogen and C_{1-4}alkyl;

or a pharmaceutically acceptable salt thereof;

with the proviso that said compound is not

1-(piperidin-4-ylcarbonyl)-4-(pyridin-2-ylcarbonyl)piperidine.

In a further aspect of the invention, there is provided a compound of formula **(Ic)**:



(Ic)

wherein:

Ring A is selected from thienyl, furyl, thiazolyl or pyridyl;

$\mathbf{R^1}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; or two R^1 on adjacent carbons may form an oxyC_{1-4}alkoxy group; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-3; wherein the values of R^1 may be the same or different;

Y is phenyl, pyridyl, thienyl, furyl or thiazolyl; wherein Y may be optionally substituted on carbon by one or more R^2;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said

heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

$\mathbf{R^3}$ and $\mathbf{R^6}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl and heterocyclyl; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

$\mathbf{R^4}$ and $\mathbf{R^7}$ are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

$\mathbf{R^8}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein $\mathbf{R^{10}}$ is selected from hydrogen and C_{1-4}alkyl;

or a pharmaceutically acceptable salt thereof;

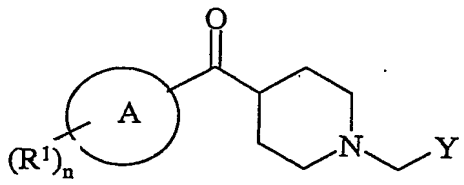
with the proviso that said compound is not

1-(2-hydroxypyrid-3-ylmethyl)-4-(thien-2-ylcarbonyl)piperidine;

1-(2-methoxypyrid-3-ylmethyl)-4-(thien-2-ylcarbonyl)piperidine or

1-benzyl-4-(thien-2-ylcarbonyl)piperidine.

In a further feature of the invention, there is provided a compound of formula (Id):



(Id)

wherein:

Ring A is phenyl;

R^1 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; or two R^1 on adjacent carbons may form an oxyC_{1-4}alkoxy group; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-3; wherein the values of R^1 may be the same or different;

Y is thienyl, furyl or thiazolyl; wherein Y may be optionally substituted on carbon by one or more R^2;

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

R^3 and **R^6** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino,

N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl and heterocyclyl; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

R^4 and **R^7** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;

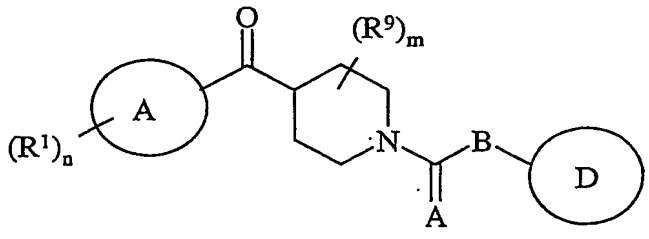
or a pharmaceutically acceptable salt thereof;

with the proviso that said compound is not

1-(thien-2-ylmethyl)-4-(4-mesylaminobenzoyl)piperidine or

1-(5-methylfur-2-ylmethyl)-4-(4-mesylaminobenzoyl)piperidine.

In a further aspect of the invention there is provided a compound of formula (**Ie**):



(**Ie**)

wherein:

Ring A is selected from carbon linked pyridyl, thienyl, furyl and thiazolyl; wherein said thiazolyl may be optionally substituted on nitrogen by a group selected from R^9;

A is O or S;

B is O or N;

Ring D is carbocyclyl or heterocyclyl; wherein Ring D may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

R^1 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-5; wherein the values of R^1 may be the same or different;

X is a direct bond, -C(O)-, -S(O)$_2$-, -C(O)NR^{11}-, -C(S)NR^{11}-, -C(O)O- or -CH$_2$-; wherein **R^{11}** is selected from hydrogen and C_{1-4}alkyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

R^3 and R^6 are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

R^4, R^5, R^7 and R^9 are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein a is 0 to 2; wherein R^{10} is selected from hydrogen and C_{1-4}alkyl;

R^{12} is methyl or ethyl;

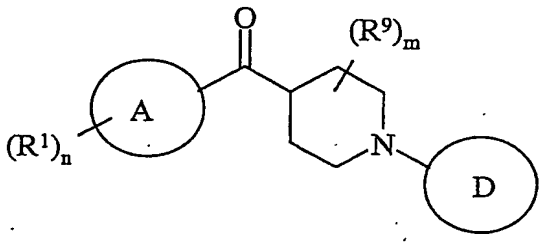
m is 0 or 1;

q is 0 or 1;

or a pharmaceutically acceptable salt thereof;

with the proviso that said compound is not 1-(2-cyano-4,5-dimethoxyanilinothiocarbonyl)-4-(thien-2-ylcarbonyl)piperidine.

In a further aspect of the invention there is provided a compound of formula (If):



(If)

wherein:

Ring A is selected from carbon linked pyridyl, thienyl, furyl and thiazolyl; wherein thiazolyl may be optionally substituted on nitrogen by a group selected from R^9;

Ring D is carbon linked phenyl, pyridyl, thienyl, furyl and thiazolyl; wherein Ring D may be optionally substituted on carbon by one or more R^2; wherein said thiazolyl may be optionally substituted on nitrogen by a group selected from R^5;

R^1 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-5; wherein the values of R^1 may be the same or different;

X is a direct bond, -C(O)-, -S(O)$_2$-, -C(O)NR^{11}-, -C(S)NR^{11}-, -C(O)O- or -CH$_2$-; wherein **R^{11}** is selected from hydrogen and C_{1-4}alkyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl,

N,*N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

R^3 and **R^6** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N*,*N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

R^4, **R^5**, **R^7** and **R^9** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N*,*N*-dimethylcarbamoyl, *N*,*N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N*,*N*-dimethylsulphamoyl, *N*,*N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;

R^{12} is methyl or ethyl;

m is 0 or 1;

q is 0 or 1;

or a pharmaceutically acceptable salt thereof.

For the avoidance of doubt, where X is -C(O)NR^{11}-, -C(S)NR^{11}- or -C(O)O- is it the C(O) or the C(S) that is attached to the nitrogen of the piperidine ring in formula (I).

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" and "C_{1-4}alkyl" includes propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals therefore "carbocyclylC_{1-4}alkyl" would include 1-carbocyclylpropyl, 2-carbocyclylethyl and 3-carbocyclylbutyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

"Heteroaryl" is a totally unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Suitably "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 8 - 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and suitable values of the term "heteroaryl" are thienyl, furyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, triazolyl, pyranyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, benzothienyl, pyridyl and quinolyl. Particularly "heteroaryl" refers to thienyl, furyl, thiazolyl, pyridyl, benzothienyl, imidazolyl or pyrazolyl.

"Aryl" is a totally unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms. Suitably "aryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "aryl" include phenyl or naphthyl. Particularly "aryl" is phenyl.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)- or a -C(S)-, or a ring sulphur atom may be optionally oxidised to form the S-oxides. Preferably a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one

atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form S-oxide(s). Examples and suitable values of the term "heterocyclyl" are thienyl, piperidinyl, morpholinyl, furyl, thiazolyl, pyridyl, imidazolyl, 1,2,4-triazolyl, thiomorpholinyl, coumarinyl, pyrimidinyl, phthalidyl, pyrazolyl, pyrazinyl, pyridazinyl, benzothienyl, benzimidazolyl, tetrahydrofuryl, [1,2,4]triazolo[4,3-a]pyrimidinyl, piperidinyl, indolyl, 1,3-benzodioxolyl and pyrrolidinyl. Further examples and suitable values of the term "heterocyclyl" are 1,3-benzodioxolyl, thienyl, furyl, thiazolyl, pyrazinyl, pyrrolyl, indolyl, quinolinyl, isoquinolinyl, pyrazolyl, isoxazolyl, benzofuranyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, pyrimidinyl, 2,1-benzisoxazolyl, 4,5,6,7-tetrahydro-2*H*-indazolyl, imidazo[2,1-*b*][1,3]thiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, 2,3-dihydro-1-benzofuryl, 2,3-dihydro-1,4-benzodioxinyl and pyridyl.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. Preferably "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. Particularly "carbocyclyl" is cyclohexyl, phenyl, naphthyl or 2-6-dioxocyclohexyl. More particularly "carbocyclyl" is phenyl, naphthyl, cyclopropyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydronaphthyl or indenyl.

An example of "C_{1-4}alkanoyloxy" is acetoxy. Examples of "C_{1-4}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-4}alkoxy" include methoxy, ethoxy and propoxy. Examples of "oxyC_{1-4}alkoxy" include oxymethoxy, oxyethoxy and oxypropoxy. Examples of "C_{1-4}alkanoylamino" include formamido, acetamido and propionylamino. Examples of and "C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of and "C_{1-4}alkylsulphonyl" include mesyl and ethylsulphonyl. Examples of "C_{1-4}alkanoyl" include propionyl and acetyl. Examples of "*N*-(C_{1-4}alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-4}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-4}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-4}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-4}alkyl)sulphamoyl" are

N-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-4}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-4}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-4}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C_{1-4}alkylsulphonylamino" are mesylamino and ethylsulphonylamino. Examples of "C_{0-4}alkylene" are a direct bond, methylene and ethylene.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess 11βHSD1 inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess 11βHSD1 inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess 11βHSD1 inhibitory activity.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Ring A is aryl.

Ring A is heteroaryl; wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9.

Ring A is carbocyclyl.

Ring A is heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9.

Ring A is phenyl.

Ring A is selected from phenyl, 1,3-benzodioxolyl, thienyl, cyclopentyl, pyridyl or furyl.

Ring A is selected from phenyl, 1,3-benzodioxol-5-yl, thien-2-yl, cyclopentyl, pyrid-2-yl or fur-2-yl.

R^1 is selected from halo or C_{1-4}alkyl.

R^1 is a substituent on carbon and is selected from halo, C_{1-4}alkyl, C_{1-4}alkoxy, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; wherein R^3 is halo; and Z is $-S(O)_a-$; wherein a is 2.

R^1 is selected from fluoro, chloro or methyl.

R^1 is selected from fluoro, chloro, methoxy or methyl.

R^1 is a substituent on carbon and is selected from fluoro, chloro, bromo, methyl, *t*-butyl, propyl, methoxy, phenyl or 6-bromonaphth-2-ylsulphonyl.

n is 0-2; wherein the values of R^1 may be the same or different.

n is 0 or 1.

n is 2; wherein the values of R^1 may be the same or different.

n is 1.

n is 0.

Ring A is phenyl, n is 1 and the substituent is para to the carbonyl of formula (I).

Ring A, R^1 and n together form phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-bromophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-propylphenyl, 4-*t*-butylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-(6-bromonaphth-2-ylsulphonyl)phenyl, 4-phenylphenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2-methyl-4-fluorophenyl, 2,4-dimethylphenyl, 1,3-benzodioxol-5-yl, thien-2-yl, 5-chlorothien-2-yl, cyclopentyl, pyrid-2-yl, 6-methylpyrid-2-yl and fur-2-yl.

Ring A, R^1 and n together form 4-fluorophenyl, 4-chlorophenyl and 4-methoxyphenyl.

X is -C(O)-.

X is $-S(O)_2-$.

X is $-CH_2-$.

X is -C(O)NR^{11}-; wherein R^{11} is selected from hydrogen.

X is -C(O)NR^{11}-; wherein R^{11} is selected from C_{1-4}alkyl.

X is -C(O)NR^{11}-; wherein R^{11} is selected from methyl.

X is -C(S)NR^{11}-; wherein R^{11} is selected from hydrogen.

X is -C(S)NR^{11}-; wherein R^{11} is selected from C_{1-4}alkyl.

X is -C(O)O-.

Y is C_{1-6}alkyl; wherein Y may be optionally substituted on carbon by one or more R^2.

Y is carbocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2.

Y is heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5.

Y is phenyl, thienyl, methyl, furyl, cyclopropyl or cyclohexyl; wherein Y may be optionally substituted on carbon by one or more R^2.

Y is phenyl, thien-2-yl, methyl, fur-2-yl, cyclopropyl or cyclohexyl; wherein Y may be optionally substituted on carbon by one or more R^2.

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5.

Y is 4-methylphenyl, 4-fluorophenyl, thien-2-yl, methyl, fur-2-yl, cyclopropyl or cyclohexyl; wherein Y may be optionally substituted on carbon by one or more R^2.

R^2 is a substituent on carbon and is selected from halo or C_{1-4}alkyl.

R^2 is a substituent on carbon and is selected from fluoro or methyl.

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 or 2, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6.

R^6 is selected from halo, nitro, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonylamino, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from C_{1-4}alkyl and C_{1-4}alkoxycarbonyl.

R^8 is selected from halo.

Z is $-S(O)_a-$, -O-, -C(O)- or $-OC(O)NR^{10}-$; wherein a is 0 or 2; wherein R^{10} is selected from hydrogen.

When Y is phenyl, R^2 is para to X.

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5; wherein

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, C_{1-4}alkyl$S(O)_a$ wherein a is 0 or 2, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^6 is selected from halo, nitro, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonylamino, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from C_{1-4}alkyl and C_{1-4}alkoxycarbonyl;

R^8 is selected from halo; and

Z is $-S(O)_a-$, -O-, -C(O)- or $-OC(O)NR^{10}-$; wherein a is 0 or 2; wherein R^{10} is selected from hydrogen.

Y is hydrogen, methyl, ethyl, propyl, isopropyl, pentyl, butyl, *t*-butyl, allyl, ethynyl, phenyl, naphthyl, cyclopropyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydronaphthyl, indenyl, thienyl, furyl, thiazolyl, pyrazinyl, pyrrolyl, indolyl, quinolinyl, isoquinolinyl, pyrazolyl, isoxazolyl, benzofuranyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, pyrimidinyl, 2,1-benzisoxazolyl, 4,5,6,7-tetrahydro-2*H*-indazolyl, imidazo[2,1-*b*][1,3]thiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, 2,3-dihydro-1-benzofuryl, 2,3-dihydro-1,4-benzodioxinyl or pyridyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said pyrrolyl, indolyl, piperidinyl, morpholinyl or pyrazolyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5; wherein

R^2 is a substituent on carbon and is selected from fluoro, chloro, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, methyl, ethyl, *t*-butyl, methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, *t*-butoxy, acetyl, methylamino, dimethylamino, acetamido, methylthio, mesyl, *t*-butoxycarbonylamino, *N*-(*t*-butoxycarbonyl)-*N*-(butyl)amino, phenyl, thienyl, isoxazolyl, morpholino, pyridyl, pyrazolyl, pyrrolidinyl, indolyl, 1,3-benzodioxolyl, isoindolinyl, pyrrolyl, phenoxy, phenylthio, benzyloxy, benzoyl, benzyloxycarbonylamino, thienylcarbonyl, pyrimidin-2-ylthio and morpholinosulphonyl; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^6 is selected from fluoro, chloro, bromo, nitro, methyl, ethenyl, methoxy, *t*-butoxyoxycarbonylamino, phenyl, phenoxy and benzoyl; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from methyl, ethyl and *t*-butoxycarbonyl; and

R^8 is selected from bromo.

X and Y together form 6-chloronaphth-2-ylmethyl, benzyl, thien-2-ylmethyl, carbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diisopropylcarbamoyl, *N*-(phenyl)carbamoyl, *N*-(2-fluorophenyl)carbamoyl, *N*-(4-fluorophenyl)carbamoyl, *N*-(3,4-difluorophenyl)carbamoyl, *N*-(3-chlorophenyl)carbamoyl, *N*-(3-methylphenyl)carbamoyl, *N*-(benzyl)carbamoyl, morpholinocarbonyl, piperidin-1-ylcarbonyl, pyrid-4-yl, 4-fluorophenyl, 4-trifluoromethylphenyl, 4-acetylphenyl, 4-acetamidophenyl, 4-methoxyphenyl, pyrimidin-2-yl, phenoxycarbonyl, methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, 2-methoxyethoxycarbonyl, benzyloxycarbonyl, isopropoxycarbonyl, 4-fluorophenoxycarbonyl, 4-methoxyphenoxycarbonyl, pyrrol-2-ylcarbonyl, 4-bromopyrrol-2-ylcarbonyl, 1-methylpyrrol-2-ylcarbonyl, 4-nitropyrrol-2-ylcarbonyl, 1,5-dimethylpyrrol-2-ylcarbonyl, 2,5-dimethylpyrrol-3-ylcarbonyl, thien-2-ylcarbonyl, thien-3-ylcarbonyl, 3-chlorothien-2-ylcarbonyl, 3-methylthien-2-ylcarbonyl, 5-chlorothien-2-ylcarbonyl, 3-bromothien-2-ylcarbonyl, 5-bromothien-2-ylcarbonyl, 5-methylthien-2-ylcarbonyl, 2-chloro-3-methoxythien-4-ylcarbonyl, thien-2-ylmethylcarbonyl, 5-mesylthien-2-ylcarbonyl, fur-2-ylcarbonyl, 5-bromofur-2-ylcarbonyl, 3-methylfur-2-ylcarbonyl, fur-3-ylcarbonyl, 2,5-dimethylfur-3-ylcarbonyl, 2,3-dimethylfur-5-ylcarbonyl, 2-methylfur-3-ylcarbonyl, 2-methyl-5-*t*-butylfur-3-ylcarbonyl, 5-trifluoromethylfur-2-ylcarbonyl, pyrid-2-ylcarbonyl, cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, benzoyl, 3-methylbenzoyl, 4-methylbenzoyl, 2-ethylbenzoyl, 3-ethylbenzoyl, 4-ethylbenzoyl, 4-*t*-butylbenzoyl,

2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2-chlorobenzoyl, 3-chlorobenzoyl, 4-chlorobenzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, 2-(*t*-butoxycarbonylamino)benzoyl, 4-(*t*-butoxycarbonylamino)benzoyl, 2,3-difluorobenzoyl, 2,4-difluorobenzoyl, 2,5-difluorobenzoyl, 3,4-difluorobenzoyl, 3,5-difluorobenzoyl, 2,3,4-trifluorobenzoyl, 3,4,5-trifluorobenzoyl, 2,4,5-trifluorobenzoyl, 2,3,4,5-tetrafluorobenzoyl, 2-cyanobenzoyl, 3-cyanobenzoyl, 4-cyanobenzoyl, 2-methoxybenzoyl, 3-methoxybenzoyl, 4-methoxybenzoyl, 2,3-dimethoxybenzoyl, 2,4-dimethoxybenzoyl, 3,5-dimethoxybenzoyl, 2,3,4-trimethoxybenzoyl, 2,4,6-trimethoxybenzoyl, 2-ethoxybenzoyl, 3-ethoxybenzoyl, 4-ethoxybenzoyl, 3-propoxybenzoyl, 4-ispropoxybenzoyl, 3-(isobutoxy)benzoyl, 3-(*t*-butoxy)benzoyl, 4-(*t*-butoxy)benzoyl, 2-trifluoromethylbenzoyl, 3-trifluoromethylbenzoyl, 4-trifluoromethylbenzoyl, 4-methylaminobenzoyl, 4-dimethylaminobenzoyl, 2-methylthiobenzoyl, 4-methylthiobenzoyl, 2-nitrobenzoyl, 4-nitrobenzoyl, 3-(benzyloxycarbonylamino)benzoyl, 2-(phenethyl)benzoyl, 2-(phenoxymethyl)benzoyl, 4-(phenoxymethyl)benzoyl, 2-(trifluoromethoxy)benzoyl, 3-(trifluoromethoxy)benzoyl, 3-phenoxybenzoyl, 4-phenoxybenzoyl, 3-benzoylbenzoyl, 3-benzyloxybenzoyl, 3-(allyloxy)benzoyl, 4-pyrrol-1-ylbenzoyl, 4-(*t*-butoxycarbonylaminomethyl)benzoyl, 4-[*N*-(*t*-butoxycarbonyl)-*N*-(butyl)amino]benzoyl, 2-fluoro-5-methoxybenzoyl, 3-fluoro-4-methoxybenzoyl, 5-fluoro-2-methoxybenzoyl, 3-fluoro-4-methylbenzoyl, 2-methyl-3-fluorobenzoyl, 2-chloro-3-methoxybenzoyl, 2-methoxy-3-methylbenzoyl, 3-methoxy-4-methylbenzoyl, 2-methoxy-4-methylbenzoyl, 2-methyl-3-methoxybenzoyl, 2-methyl-4-methoxybenzoyl, 3-methyl-4-methoxybenzoyl, 2,4-dimethoxy-3-methylbenzoyl, 3-(morpholinosulphonyl)benzoyl, 4-(morpholinosulphonyl)benzoyl, 3-benzyloxy-4-methoxybenzoyl, 2-ethylbutyryl, 4-(2,4-dimethylphenyl)butyryl, 4-(indol-3-yl)butyryl, 4-(5-bromothien-2-ylcarbonyl)butyryl, 4-morpholinobenzoyl, isoxazole-5-ylcarbonyl, 3-methylisoxazole-5-ylcarbonyl, 3,5-dimethylisoxazol-4-ylcarbonyl, 4-(pyrazol-1-yl)benzoyl, thiazol-4-ylcarbonyl, 2-methylthiazol-4-ylcarbonyl, 3-chlorothiazol-5-ylcarbonyl, 2,4-dimethylthiazol-5-ylcarbonyl, 2-(pyrid-2-yl)-4-methylthiazol-5-ylcarbonyl, 2-(pyrrolidin-1-yl)pyrazin-6-ylcarbonyl, 2-phenylbenzoyl, 4-phenylbenzoyl, 2-(2-nitrophenyl)benzoyl, 3-(4-fluorophenyl)benzoyl, 4-acetylbenzoyl, indol-6-ylcarbonyl, indol-7-ylcarbonyl, 5-fluoroindol-2-ylcarbonyl, 1-methylindol-3-ylcarbonyl, 3-methylindol-1-ylcarbonyl, 5-methoxyindol-2-ylcarbonyl, isoquinoline-1-ylcarbonyl, quinoline-2-ylcarbonyl, quinoline-3-ylcarbonyl,

quinoline-4-ylcarbonyl, quinoline-6-ylcarbonyl, 2-methylquinoline-6-ylcarbonyl, 3-methylinden-2-ylcarbonyl, 1,2,3,4-tetrahydronaphth-5-ylcarbonyl, benzofuran-2-ylcarbonyl, 1,2,3-thiadiazol-4-ylcarbonyl, 1,2,5-thiadiazol-3-ylcarbonyl, pyrazol-3-ylcarbonyl, 1-methylpyrazol-3-ylcarbonyl, 5-methylpyrazol-3-ylcarbonyl, 1,5-dimethylpyrazol-3-ylcarbonyl, 1-ethyl-3-methylpyrazol-5-ylcarbonyl, 1-methyl-5-chloropyrazol-4-ylcarbonyl, 1-methyl-3-*t*-butylpyrazol-5-ylcarbonyl, 2,1-benzisoxazol-3-ylcarbonyl, 2-(2-chlorophenyl)ethynylcarbonyl, 3-(5-bromo-1,3-benzodioxol-6-yl)propionyl, 2-methylpropionyl, 2,2-dimethylpropionyl, 2-ethylheptanoyl, 4,5,6,7-tetrahydro-2*H*-indazol-3-ylcarbonyl, 6-methylimidazo[2,1-*b*][1,3]thiazol-5-ylcarbonyl, *N*-(*t*-butoxycarbonyl)piperidin-3-ylcarbonyl, *N*-(*t*-butoxycarbonyl)piperidin-4-ylcarbonyl, *N*-(*t*-butoxycarbonyl)morpholin2-ylcarbonyl, tetrahydrofuran-2-ylcarbonyl, tetrahydrofuran-3-ylcarbonyl, 2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl, tetrahydropyranylcarbonyl, 2,3-dihydro-1-benzofur-2-ylcarbonyl, acetyl, (3,5-dimethylisoxazol-4-yl)acetyl, (4-fluorophenyl)acetyl, (2-nitrophenyl)acetyl, (4-bromobenzoylmethylthio)acetyl, (2,4-dichloro-6-methoxyphenoxy)acetyl, (2-nitro-4-chlorophenylthio)acetyl, (pyrimidin-2-ylthio)acetyl, (isoindolin-2-yl)acetyl, thien-2-ylsulphonyl, mesyl, ethylsulphonyl, isopropylsulphonyl, butylsulphonyl, 2-methylphenylsulphonyl, 3-methylphenylsulphonyl, 4-methylphenylsulphonyl, 2,5-dimethylphenylsulphonyl, 4-ethylphenylsulphonyl, 3-methoxyphenylsulphonyl, 4-methoxyphenylsulphonyl, 2-fluorophenylsulphonyl, 3-fluorophenylsulphonyl, 4-fluorophenylsulphonyl, 2-chlorophenylsulphonyl, 3-chlorophenylsulphonyl, 4-chlorophenylsulphonyl, 2-bromophenylsulphonyl, 3-bromophenylsulphonyl, 4-bromophenylsulphonyl, 2-trifluoromethylsulphonyl, 3-trifluoromethylsulphonyl, 4-trifluoromethylsulphonyl, 4-acetamidophenylsulphonyl, 2,4-difluorophenylsulphonyl, 2,6-difluorophenylsulphonyl, 2,4,5-trifluorophenylsulphonyl, 2-cyanophenylsulphonyl, 2-chloro-4-fluorophenylsulphonyl, 2-chloro-6-methylphenylsulphonyl, 3-fluoro-6-methylphenylsulphonyl, 2-methoxy-5-methylphenylsulphonyl, 2-nitro-4-methoxyphenylsulphonyl, 3-chloro-4-aminophenylsulphonyl, 2-chloro-4-cyanophenylsulphonyl, benzylsulphonyl, 4-fluorobenzylsulphonyl, thien-3-ylsulphonyl, 5-chlorothien-2-ylsulphonyl, 2,5-dichlorothien-3-ylsulphonyl, 1,3-dimethyl-5-chloropyrazol-4-ylsulphonyl, 3,5-dimethylisoxazol-4-ylsulphonyl and (4-fluoroanilino)thiocarbonyl.

R^{12} is 4-methyl.

R^{12} is 4-ethyl.

R^{12} is 3-methyl.

m is 0.

m is 1.

q is 0.

q is 1.

According to a further feature of the invention there is provided the use of a compound of formula (I) wherein:

Ring A is phenyl;

R^1 is selected from halo or C_{1-4}alkyl;

n is 1;

X is -C(O)-, $-S(O)_2-$ or $-CH_2-$;

Y is phenyl, thienyl, methyl, furyl, cyclopropyl or cyclohexyl; wherein Y may be optionally substituted on carbon by one or more R^2; and

R^2 is a substituent on carbon and is selected from halo or C_{1-4}alkyl;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

According to a further feature of the invention there is provided the use of a compound of formula (I) wherein:

Ring A is selected from phenyl, 1,3-benzodioxolyl, thienyl, cyclopentyl, pyridyl or furyl;

R^1 is a substituent on carbon and is selected from halo, C_{1-4}alkyl, C_{1-4}alkoxy, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; wherein R^3 is halo; and Z is $-S(O)_a-$; wherein a is 2;

n is 0-2; wherein the values of R^1 may be the same or different;

X is a direct bond, -C(O)-, $-S(O)_2-$, $-C(O)NR^{11}-$, $-C(S)NR^{11}-$, -C(O)O- or $-CH_2-$; wherein R^{11} is selected from hydrogen and methyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5; wherein

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 or 2, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^6 is selected from halo, nitro, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonylamino, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from C_{1-4}alkyl and C_{1-4}alkoxycarbonyl;

R^8 is selected from halo; and

Z is -S(O)$_a$-, -O-, -C(O)- or -OC(O)NR^{10}-; wherein a is 0 or 2; wherein R^{10} is selected from hydrogen;

R^{12} is methyl or ethyl;

m is 0 or 1; and

q is 0 or 1;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

In another aspect of the invention, suitable compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt thereof.

In another aspect of the invention, suitable compounds of the invention are any one of the Reference Examples or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention there is provided a compound selected from:

1-[2-hydroxy-2-(2,3-dihydro-1,4-benzodioxin-2-yl)ethyl]-4-(4-fluorobenzoyl)piperidine;

1-(7-methyl-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-4-(benzoyl)piperidine;

1-(6-fluoro-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-4-(benzoyl)piperidine;

1-(7-fluoro-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-4-(benzoyl)piperidine;

1-[2-(6-methoxynaphth-2-yl)propionyl]-4-(4-fluorobenzoyl)piperidine;

1-(4-bromoindol-2-ylcarbonyl)-4-(benzoyl)piperidine; and

1-(3-phenyl-5-methylisoxazol-4-ylcarbonyl)-4-(4-fluorobenzoyl)piperidine;

or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention there is provided the use of a compound selected from:

1-[2-((1*H*,3*H*)-2,4-dioxoquinazolin-3-yl)ethyl]-4-(4-fluorobenzoyl)piperidine;

1-[3-(napath-1-yloxy)propyl]-4-(4-fluorobenzoyl)piperidine;

1-[2-(2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]-4-(4-fluorobenzoyl)piperidine;

4-(4-fluorobenzoyl)piperidine;

1-(*t*-butoxycarbonyl)-4-(benzoyl)piperidine;

1-(acetyl)-4-(4-fluorobenzoyl)piperidine;

1-(*t*-butoxycarbonyl)-4-(4-fluorobenzoyl)piperidine;

1-(2,4-trifluoromethyl-6-methoxybenzoyl)-4-(4-chlorobenzoyl)piperidine;

1-(3,4-dichlorophenylsulphonyl)-4-(4-methylbenzoyl)piperidine;

1-(2-nitro-4-trifluoromethylphenyl)-4-(benzoyl)piperidine;

1-(anilinocarbonyl)-4-(benzoyl)piperidine;

1-[3-(2,6-dichlorophenyl)-5-methylisoxazol-4-ylcarbonyl]-4-(benzoyl)piperidine;

1-(4-chlorobenzoyl)-4-(benzoyl)piperidine;

1-[(5-trifluoromethylpyrid-2-ylthio)acetyl]-4-(benzoyl)piperidine;

1-[(4-chlorophenylthio)acetyl]-4-(benzoyl)piperidine;

1-(fur-2-ylcarbonyl)-4-(benzoyl)piperidine;

1-(4-methyl-1,2,3-thiadiazol-5-ylcarbonyl)-4-(benzoyl)piperidine;

1-(thien-2-ylcarbonyl)-4-(benzoyl)piperidine;

1-(3-trifluoromethylbenzoyl)-4-(benzoyl)piperidine;

1-(propylaminothiocarbonyl)-4-(4-methylbenzoyl)piperidine;

1-(5-nitrofur-2-ylcarbonyl)-4-(2,3,4,5,6-pentamethylbenzoyl)piperidine;

1-(3,5-ditrifluoromethylphenylsulphonyl)-4-(4-methylbenzoyl)piperidine;

1-(3,5-dimethylisoxazol-4-ylsulphonyl)-4-(4-methylbenzoyl)piperidine;

1-(2,6-difluorobenzoyl)-4-(benzoyl)piperidine;

1,4-bis-(4-methylbenzoyl)piperidine;

1-(3,5-ditrifluoromethylphenylsulphonyl)-4-(2,4-difluorobenzoyl)piperidine;

1-(2,4-difluorophenylsulphonyl)-4-(2,4-difluorobenzoyl)piperidine;

1-(4-methylbenzoyl)-4-(2,4,6-trimethylbenzoyl)piperidine;

1-(4-chlorophenylsulphonyl)-4-(benzoyl)piperidine;

1-[2-((1*H*,3*H*)-2-thiocarbonyl-4-oxoquinazolin-3-yl)ethyl]-4-(4-fluorobenzoyl)piperidine;

1-(trifluoroacetyl)-4-(benzoyl)piperidine;

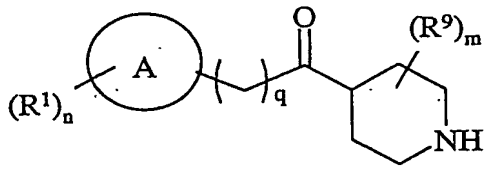
1-(3,5-dimethylisoxazol-4-ylsulphonyl)-4-(benzoyl)piperidine;

1-(4-*t*-butylbenzoyl)-4-(benzoyl)piperidine;

1-(2,4-dimethylthiazol-5-ylsulphonyl)-4-(benzoyl)piperidine;
1-[(4-chlorophenylsulphonyl)acetyl]-4-(benzoyl)piperidine;
1-(4-chloroanilinocarbonyl)-4-(benzoyl)piperidine; 1-[3-methyl-4-(4-chlorophenylsulphonyl)thien-2-ylcarbonyl]-4-(4-fluorobenzoyl)piperidine;
1-(thien-2-ylcarbonyl)-4-(2,4-difluorobenzoyl)piperidine;
1-[1-(4-isobutylphenyl)ethyl]-4-(benzoyl)piperidine;
1-{1-[4-(4-trifluoromethylphenoxy)phenoxy]ethyl}-4-(benzoyl)piperidine;
1-(3,5-ditrifluoromethylanilinothiocarbonyl)-4-(4-methylbenzoyl)piperidine;
1-(2-methyl-4-bromoanilinothiocarbonyl)-4-(4-methylbenzoyl)piperidine;
1-(4-fluoroanilinothiocarbonyl)-4-(4-methylbenzoyl)piperidine;
1-(thien-2-ylcarbonyl)-4-(2,4,6-trimethylbenzoyl)piperidine;
1-(cyclobutylcarbonyl)-4-(benzoyl)piperidine;
1-(2,4-dichloroanilinothiocarbonyl)-4-(4-methylbenzoyl)piperidine;
or a pharmaceutically acceptable salt thereof;
in the manufacture of a medicament for use in the inhibition of 11βHSD1.

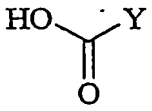
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

Process 1) for compounds of formula (I) wherein X is -C(O)-; reacting an amine of formula (II):



(II)

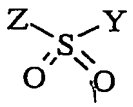
with an acid of formula (III):



(III)

or an activated derivative thereof;

Process 2) for compounds of formula (I) wherein X is -$S(O)_2$-; reacting an amine of formula (II) with a sulphonyl halide of formula (IV):



(IV)

wherein Z is fluoro or chloro;

Process 3) for compounds of formula (I) wherein X is -CH_2-; reacting an amine of formula (II) with a compound of formula (V):

(V)

wherein L is a displaceable group; or

Process 4) for compounds of formula (I) wherein X is -CH_2-; reducing a compound of formula (I) wherein X is -C(O)-;

Process 5) for compounds of formula (I) wherein X is a direct bond; reacting an amine of formula (II) with a compound of formula (VI):

L-Y

(VI)

Process 6) for compounds of formula (I) wherein X is -C(O)NR^{11}- and R^{11} is hydrogen; reacting an amine of formula (II) with an isocyanate of formula (VII):

O=C=N-Y

(VII)

Process 7) for compounds of formula (I) wherein X is -C(S)NR^{11}- and R^{11} is hydrogen; reacting an amine of formula (II) with an isothiocyanate of formula (VIII):

S=C=N-Y

(VIII)

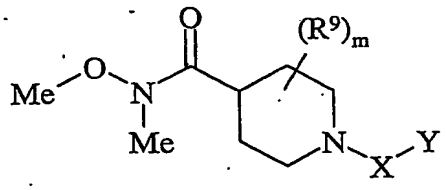
Process 8) for compounds of formula (I) wherein X is -C(O)O-; reacting an amine of formula (II) with a compound of formula (IX):

L-C(O)-O-Y

(IX)

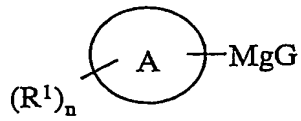
wherein L is a displaceable group;

Process 9) for compounds of formula (I) wherein q is 0; reacting a Weinreb amide of the formula (X):



(X)

with a compound of formula (XI):



wherein G is a displaceable group;

and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt thereof.

L is a displaceable group, suitable values for L include halo, particularly chloro or bromo, or mesyloxy.

G is a displaceable group. Suitable values for G include bromo.

The reactions described above may be performed under standard conditions known to the person skilled in the art. The intermediates described above are commercially available, are known in the art or may be prepared by known procedures.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic

hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possess 11βHSD1 inhibitory activity. These properties may be assessed using the following assay.

Assay

HeLa cells (human cervical carcinoma derived cells) were stably transfected with a construct containing four copies of the glucocorticoid response element (GRE) linked to a beta-galactosidase reporter gene (3 kb lac Z gene derived from pSV-B-galactosidase). These cells were then further stably transfected with a construct containing full-length human 11βHSD1 enzyme (in pCMVHyg) to create GRE4-βGal/11βHSD1 cells. The principal of the assay is as follows. Cortisone is freely taken up by the cells and is converted to cortisol by 11βHSD1 oxo-reductase activity and cortisol (but not cortisone) binds to and activates the glucocorticoid receptor. Activated glucocorticoid receptor then binds to the GRE and initiates transcription and translation of β-galactosidase. Enzyme activity can then be assayed with high sensitivity by colourimetric assay. Inhibitors of 11βHSD1 will reduce the conversion of cortisone to cortisol and hence decrease the production of β-galactosidase.

Cells were routinely cultured in DMEM (Invitrogen, Paisley, Renfrewshire, UK) containing 10% foetal calf serum (LabTech), 1% glutamine (Invitrogen), 1% penicillin & streptomycin (Invitrogen), 0.5 mg/ml G418 (Invitrogen) & 0.5mg/ml hygromycin (Boehringer). Assay media was phenol red free-DMEM containing 1% glutamine, 1% penicillin & streptomycin.

Compounds (1mM) to be tested were dissolved in dimethyl sulphoxide (DMSO) and serially diluted into assay media containing 10% DMSO. Diluted compounds were then plated into transparent flat-bottomed 384 well plates (Matrix, Hudson NH, USA).

The assay was carried out in 384 well microtitre plate (Matrix) in a total volume of 50μl assay media consisting of cortisone (Sigma, Poole, Dorset, UK, 1μM), HeLa

GRE4-βGal/11βHSD1 cells (10,000 cells) plus test compounds (3000 to 0.01 nM). The plates were then incubated in 5% O_2, 95% CO_2 at 37°C overnight.

The following day plates were assayed by measurement of β-galactosidase production. A cocktail (25µl) consisting of 10X Z-buffer (600 mM Na_2HPO_4, 400 mM $NaH_2PO_4.2H_2O$, 100 mM KCl, 10 mM $MgSO_4.7H_2O$, 500 mM β-mercaptoethanol, pH 7.0), SDS (0.2%), chlorophenol red-β-D-galactopyranoside (5mM, Roche Diagnostics) was added per well and plates incubated at 37°C for 3-4hours. β-Galactosidase activity was indicated by a yellow to red colour change (absorbance at 570nm) measured using a Tecan Spectrafluor Ultra.

The calculation of median inhibitory concentration (IC_{50}) values for the inhibitors was performed using Origin 6.0 (Microcal Software, Northampton MA USA). Dose response curves for each inhibitor were plotted as OD units at each inhibitor concentration with relation to a maximum signal (cortisone, no compound) and IC_{50} values calculated. Compounds of the present invention typically show an IC_{50} <10µM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(Ia)**, **(Ib)**, **(Ic)**, **(Id)**, **(Ie)** or **(If)**or a pharmaceutically acceptable salt thereof or of the Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 0.1 – 50 mg/kg that normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-1000 mg of active ingredient. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

We have found that the compounds defined in the present invention, or a

pharmaceutically acceptable salt thereof, are effective 11βHSD1inhibitors, and accordingly have value in the treatment of disease states associated with metabolic syndrome.

It is to be understood that where the term "metabolic syndrome" is used herein, this relates to metabolic syndrome as defined in 1) and/or 2) or any other recognised definition of this syndrome. Synonyms for "metabolic syndrome" used in the art include Reaven's Syndrome, Insulin Resistance Syndrome and Syndrome X. It is to be understood that where the term "metabolic syndrome" is used herein it also refers to Reaven's Syndrome, Insulin Resistance Syndrome and Syndrome X.

According to a further aspect of the present invention there is provided a compound of formula **(Ia)**, **(Ib)**, **(Ic)**, **(Id)**, **(Ie)** or **(If)** or a pharmaceutically acceptable salt thereof or of the Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

Thus according to this aspect of the invention there is provided a compound of formula **(Ia)**, **(Ib)**, **(Ic)**, **(Id)**, **(Ie)** or **(If)** or a pharmaceutically acceptable salt thereof or of the Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use as a medicament.

According to another feature of the invention there is provided the use of a compound of the formula of formula **(Ia)**, **(Ib)**, **(Ic)**, **(Id)**, **(Ie)** or **(If)** or a pharmaceutically acceptable salt thereof or of the Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound selected from the Reference Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man.

Where production of or producing an 11βHSD1 inhibitory effect is referred to suitably this refers to the treatment of metabolic syndrome. Alternatively, where production of an 11βHSD1 inhibitory effect is referred to this refers to the treatment of diabetes, obesity, hyperlipidaemia, hyperglycaemia, hyperinsulinemia or hypertension, particularly diabetes and obesity. Alternatively, where production of an 11βHSD1 inhibitory effect is referred to this refers to the treatment of glaucoma, osteoporosis, tuberculosis, dementia, cognitive disorders or depression.

According to a further feature of this aspect of the invention there is provided a method for producing an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

According to a further feature of this aspect of the invention there is provided a method for producing an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (Ia), (Ib), (Ic), (Id), (Ie) or (If) or a pharmaceutically acceptable salt thereof or of the Examples, or a pharmaceutically acceptable salt thereof.

According to a further feature of this aspect of the invention there is provided a method for producing an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound selected from the Reference Examples, or a pharmaceutically acceptable salt thereof.

In addition to their use in therapeutic medicine, the compounds of formula (I), or a pharmaceutically acceptable salt thereof, are also useful as pharmacological tools in the development and standardisation of in vitro and *in vivo* test systems for the evaluation of the effects of inhibitors of 11βHSD1 in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

The inhibition of 11βHSD1 described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example agents than might be co-administered with 11βHSD1 inhibitors, particularly those of the present invention, may include the following main categories of treatment:

1) Insulin and insulin analogues;
2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide) and prandial glucose regulators (for example repaglinide, nateglinide);
3) Insulin sensitising agents including PPARγ agonists (for example pioglitazone and rosiglitazone);
4) Agents that suppress hepatic glucose output (for example metformin);

5) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);

6) Agents designed to treat the complications of prolonged hyperglycaemia; e.g. aldose reductase inhibitors

7) Other anti-diabetic agents including phosotyrosine phosphatase inhibitors, glucose 6 - phosphatase inhibitors, glucagon receptor antagonists, glucokinase activators, glycogen phosphorylase inhibitors, fructose 1,6 bisphosphastase inhibitors, glutamine:fructose -6-phosphate amidotransferase inhibitors

8) Anti-obesity agents (for example sibutramine and orlistat);

9) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); ileal bile acid absorption inhibitors (IBATi), cholesterol ester transfer protein inhibitors and nicotinic acid and analogues (niacin and slow release formulations);

10) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); calcium antagonists (eg. nifedipine); angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);

11) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin; and

12) Anti-inflammatory agents, such as non-steroidal anti-infammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated in the following non limiting Examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these Examples may be used where appropriate, and in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) all reactions were carried out under an inert atmosphere at ambient temperature, typically in the range 18-25°C, with solvents of HPLC grade under anhydrous conditions, unless otherwise stated;

(iii) column chromatography (by the flash procedure) was performed on Silica gel 40-63 μm (Merck);

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic resonance chemical shift values were measured in deuterated $CDCl_3$ (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer unless otherwise stated data was recorded at 400MHz; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; ABq, AB quartet; ABd, AB doublet, ABdd, AB doublet of doublets; dABq, doublet of AB quartets; LCMS were recorded on a Waters ZMD, LC column xTerra MS C_8(Waters), detection with a HP 1100 MS-detector diode array equipped; mass spectra (MS) (loop) were recorded on VG Platform II (Fisons Instruments) with a HP-1100 MS-detector diode array equipped; unless otherwise stated the mass ion quoted is (MH^+);

(vi) unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Cromasil C_8, 7 μm, (Akzo Nobel); MeCN and de-ionised water 10 mM ammonium acetate as mobile phases, with suitable composition;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis;

(viii) where solutions were dried sodium sulphate was the drying agent;

(ix) where an "ISOLUTE-Si" column is referred to, this means a column containing 1 or 2 g of silica, the silica being contained in a 6 ml disposable syringe and supported by a porous disc of 54Å pore size, obtained from International Sorbent Technology under the name "ISOLUTE"; "ISOLUTE" is a registered trade mark;

(x) the following abbreviations may be used hereinbefore or hereinafter:-

DCM	dichloromethane;
MeCN	acetonitrile;

THF	tetrahydrofuran;
HATU	O-(7-azabenzotriazol-1-yl)-n,n,n',n'-tetramethyluronium hexafluoro-phosphate;
PS-DIEA	Polymer Supported-Diisopropylethylamine (From Argonaut Technologies);
DIEA	Diisopropylethylamine;
PS-Trisamine	Tris-(2-aminoethyl)amine polystyrene;
TFA	trifluoroacetic acid; and
EtOAc	ethyl acetate.

xi) where an Isolute SCX-2 column is referred to, this means an "ion exchange" extraction cartridge for adsorption of basic compounds, i.e. a polypropylene tube containing a benzenesulphonic acid based strong cation exchange sorbent, used according to the manufacturers instructions obtained from International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ;

xii) where an Isolute amine column is referred to, this means an "ion exchange" extraction cartridge for adsorption of acidic compounds, i.e. a polypropylene tube containing a amino silane covalently bonded to a silica particle used according to the manufacturers instructions obtained from International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ;

xiii) where Mettler Toledeo Myriad ALLEX liquid –liquid extractor is referred to this means an automated liquid liquid extraction workstation capable of separating aqueous and organic phases; and

xiv) where as Isco CombiFlash Optix-10 parallel flash chromatography system is referred to this means an automated chromatography workstation capable of carrying out up to 10 purifications in parallel via flash chromatography using pre packed silica cartridges.

Example 1

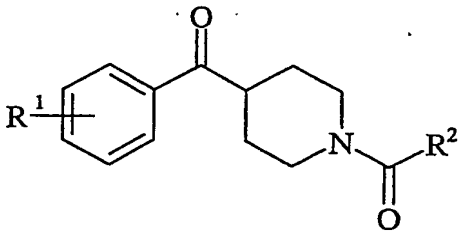
1-(4-Fluorobenzoyl)-4-(4-chlorobenzoyl)piperidine

To a stirred solution of (4-chlorophenyl)(4-piperidyl)methanone hydrochloride (187mg, 0.72mmol) and triethylamine (240µl, 1.71mmol) in DCM (3ml) was added 4-fluorobenzoyl chloride (109mg, 0.69mmol). The reaction was left to stir at room temperature for one hour then transferred to a sep funnel and diluted to approximately 10ml with DCM. This solution was washed with 2M HCl (5ml), water (5ml) and brine (5ml) then dried, filtered and evaporated to yield product as a solid (70mg, 29%). NMR (DMSO-d_6, 100°C): 1.60 (m,

2H), 1.85 (m, 2H), 3.15 (t, 2H), 3.65 (m, 1H), 4.00 (m, 2H), 7.20 (t, 2H), 7.45 (m, 2H), 7.55 (d, 2H), 7.95 (d, 2H); m/z: 346.

Examples 2-15 and Reference Examples 1-2

The procedure described in Example 1 was repeated using the appropriate reagent to replace the "4-fluorobenzoyl chloride" to obtain the compounds described below. In some cases a base wash was also carried out ($NaHCO_3$) prior to washing with brine.



Ex	R^1	R^2	NMR	M/z
2	4-Cl	Cyclohexyl	1.25 (br m, 4H), 1.40-2.00 (br m, 10H), 2.50 (m, 1H), 2.80 (br t, 1H), 3.20 (br t, 1H), 3.45 (m, 1H), 4.00 (br m, 1H), 4.60 (br m, 1H), 7.45 (d, 2H), 7.90 (d, 2H)	334
3	4-Cl	4-Methyl-phenyl	0.85 (br m, 1H), 1.25 (s, 1H), 1.80 (m, 4H), 2.35 (s, 3H), 3.10 (br m, 2H), 3.50 (m, 1H), 7.20 (d, 2H), 7.30 (d, 2H), 7.45 (d, 2H), 7.90 (d, 2H)	342
4	4-Cl	fur-2-yl	1.80-2.00 (br m, 4H), 3.20 (br m, 2H), 3.50 (m, 1H), 4.56 (d, 2H), 6.45 (m, 1H), 7.00 (d, 1H), 7.45 (d, 3H), 7.90 (d, 2H)	318
5	4-Cl	Cyclopropyl	0.85 (m, 2H), 1.00 (m, 2H), 1.65-2.00 (br m, 5H), 2.90 (br m, 1H), 3.30 (br m, 1H), 3.50 (m, 1H), 4.30 (br s, 1H), 4.55 (br s, 1H), 7.45 (d, 2H), 7.90 (d, 2H)	292
6	4-F	Furan	1.90 (br m, 4H), 3.20 (br m, 2H), 3.50 (m, 1H), 4.50 (d, 2H), 6.50 (m, 1H), 6.95 (d, 1H), 7.15 (t, 2H), 7.50 (s, 1H), 8.00 (m, 2H)	302
7	4-F	Cyclohexyl	1.30 (br m, 3H), 1.40-2.00 (br m, 11H+H20), 2.50 (m, 1H), 2.80 (m, 1H), 3.20 (m, 1H), 3.45 (m, 1H), 4.00 (m, 1H), 4.60 (m, 1H), 7.15 (t, 2H), 7.95 (m, 2H)	318

Ex	R^1	R^2	NMR	M/z
8	4-F	4-Fluoro-phenyl	1.85 (br s, 4H), 3.10 (br m, 2H), 3.50 (m, 1H), 7.10 (m, 4H), 7.45 (m, 2H), 8.00 (m, 2H)	330
9	4-F	Cyclopropyl	0.75 (m, 2H), 1.00 (m, 2H), 1.75-2.00 (br m, 5H), 2.85 (br m, 1H), 3.30 (br m, 1H), 3.50 (m, 1H), 4.30 (br m, 1H), 4.55 (br m, 1H), 7.10 (t, 2H), 7.95 (m, 2H)	276
RE1	4-Me	Thien-2-yl	DMSO-d_6: 1.50 (m, 2H), 1.85 (m, 2H), 2.35 (s, 3H), 3.20 (m, 2H), 3.75 (m, 1H), 4.30 (br d, 2H), 7.10 (t, 1H), 7.33 (d, 2H), 7.38 (d, 1H), 7.75 (d, 1H), 7.90 (d, 2H)	314
10	4-F	Thien-2-yl	1.55 (m, 2H), 1.85 (m, 2H), 3.20 (m, 2H), 3.80 (m, 1H), 4.30 (br d, 2H), 7.10 (m, 1H), 7.35 (m, 3H), 7.70 (m, 1H), 8.10 (m 2H)	318
11	4-Cl	Thien-2-yl	1.50 (m, 2H), 1.85 (br d, 2H), 3.20 (m, 2H), 3.75 (m, 1H), 4.30 (br d, 2H), 7.10 (m, 1H), 7.35 (d, 1H), 7.60 (d, 2H), 7.75 (d, 1H), 8.00 (d, 2H)	334
RE2	4-Cl	Acetyl		266
12	4-OMe	Fur-2-yl	1.85 (m, 4H), 3.10 (br s, 2H), 3.45 (m, 1H), 3.80 (s, 3H), 4.45 (br d, 2H), 6.40 (m, 1H), 6.90 (m, 3H), 7.40 (s, 1H), 7.90 (d, 2H)	314
13	4-OMe	4-Fluoro-phenyl		342
14	4-OMe	Cyclopropyl	0.75 (m, 2H), 1.00 (m, 2H), 1.75 (m, 2H)1.90 (m, 3H), 2.90 (br s, 1H), 3.30 (br s, 1H), 3.50 (m, 1H), 3.85 (s, 3H), 4.30 (br s, 1H), 4.55 (br s, 1H), 6.95 (d, 2H), 7.95 (d, 2H)	288
15 [1]	4-F	4-Fluoro-benzyl	(DMSO-d_6): 1.35 (m, 2H), 1.75 (m, 2H), 2.75 (t, 1H), 3.15 (t, 1H), 3.65 (m, 1H), 3.70 (s, 2H), 4.00 (d, 1H), 4.40 (d, 1H), 7.10 (t, 2H), 7.25 (m, 2H), 7.35 (t, 2H), 8.05 (m, 2H)	344

[1] Purified by column chromatography (10g Silica, 40% EtOAc/isohexane)

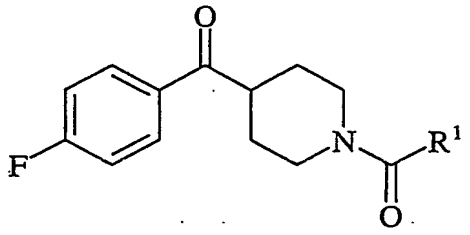
Example 16

1-(5-Chlorothien-2-ylcarbonyl)-4-(4-fluorobenzoyl)piperidine

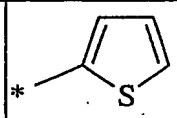
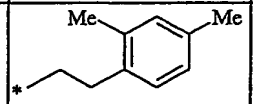
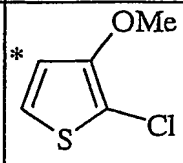
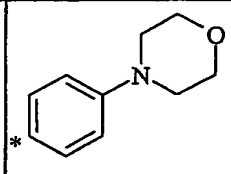
To a stirred solution of 5-chlorothiophene-2-carboxylic acid (35.5mgs, 0.2mmol) in DCM (8 ml) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (57.5mgs, 0.3mmol) and N, N diisopropylethylamine (69.7mgs, 0.5mmol) and the mixture was stirred for 15mins. 4-(4-Fluorobenzoyl)piperidine hydrochloride (58mgs, 0.24mmol) was added and the reaction was stirred for 16hours at room temperature. The solution was washed with 2M HCl (5ml), saturated sodium carbonate (5ml), water (5ml), using a Mettler Toledeo Myriad ALLEX liquid –liquid extractor, then dried, filtered and evaporated to yield the product as a solid (33.6mgs, 43%). M/z 351.

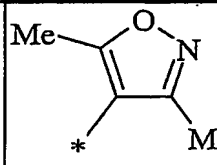
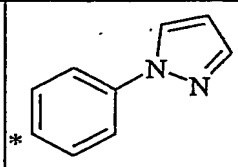
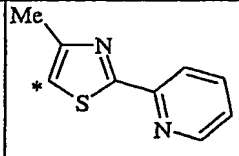
Examples 17-121

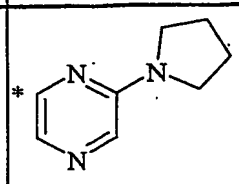
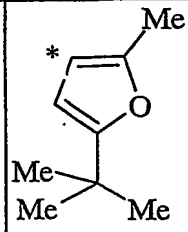
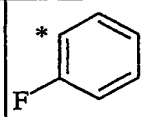
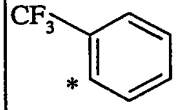
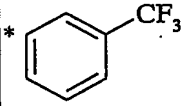
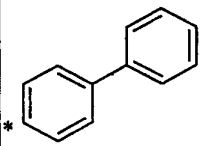
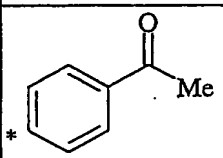
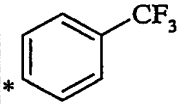
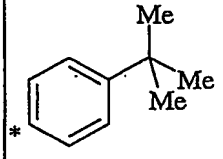
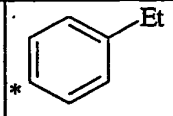
The following compounds were prepared by the procedure of Example 16. "*" indicates the carbon atom that is attached to the carbonyl of formula (A).



(A)

Ex	R^1	M/z
17		331
18		381
19		381
20		396

Ex	R^1	M/z
21		344
22		377
23		409

Ex	R^1	M/z
24		382
25		371
26		329
27		379
28		379
29		387
30		353
31		379
32		367
33		339

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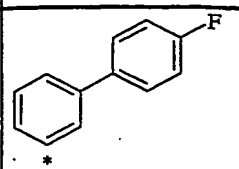
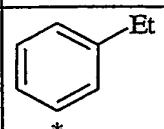
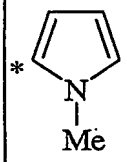
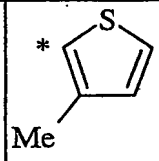
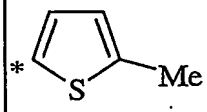
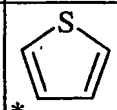
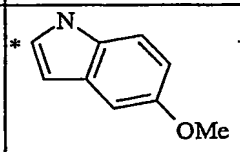
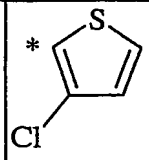
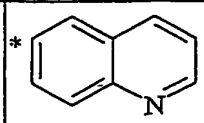
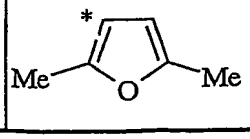
34		405
35		339
36		314
37		331
38		331
39		317
40		380
41		351
42		362
43		329

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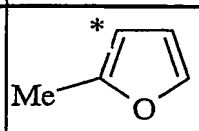
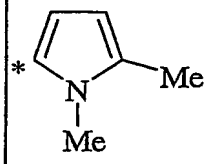
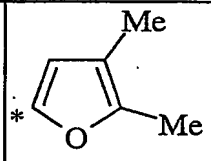
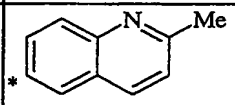
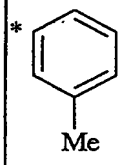
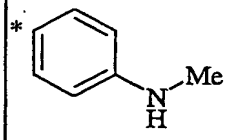
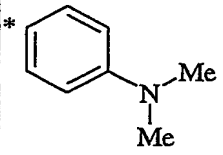
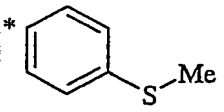
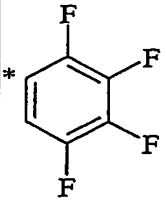
44		315
45		328
46		329
47		376
48		325
49		340
50		354
51		357
52		383

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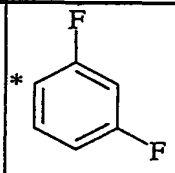
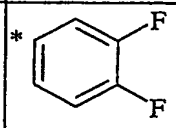
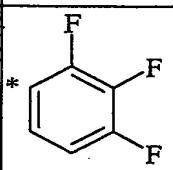
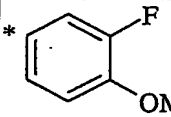
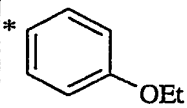
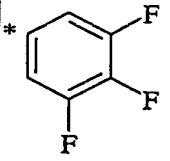
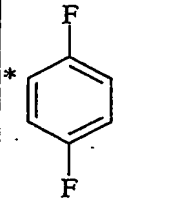
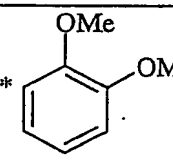
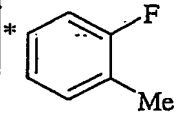
53		347
54		347
55		365
56		359
57		355
58		365
59		347
60		371
61		343

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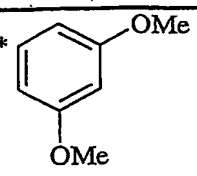
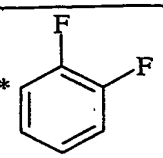
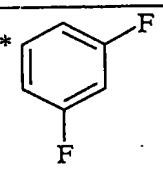
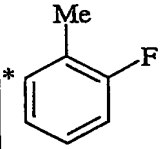
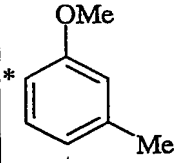
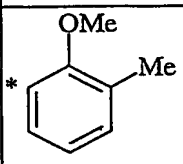
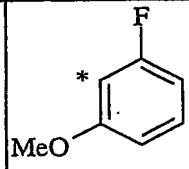
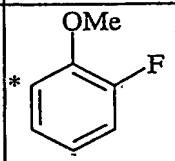
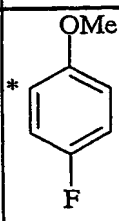
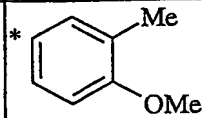
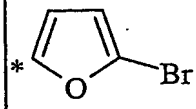
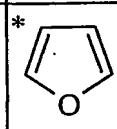
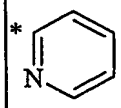
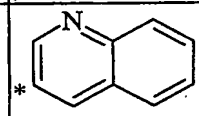
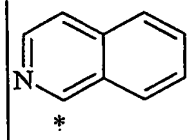
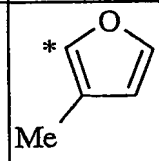
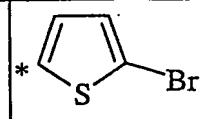
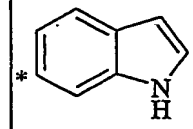
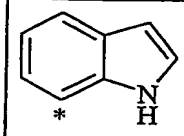
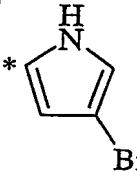
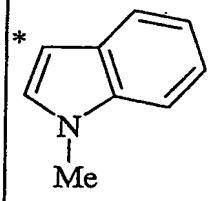
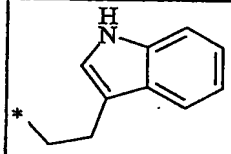
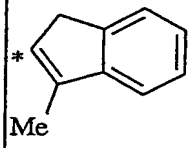
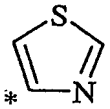
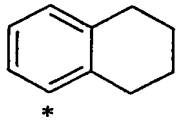
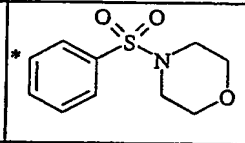
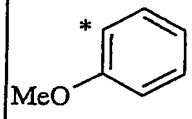
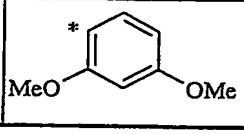
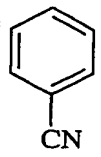
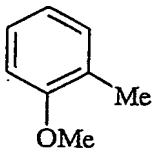
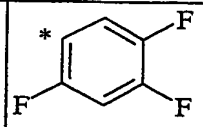
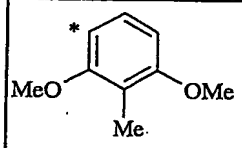
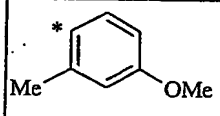
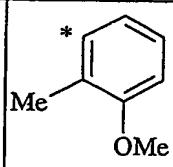
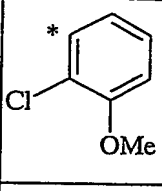
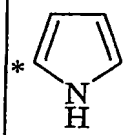
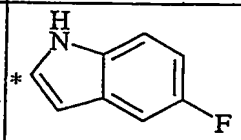
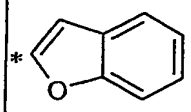
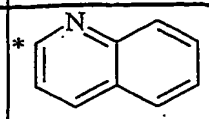
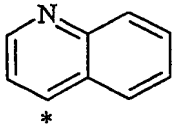
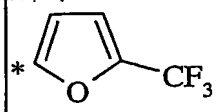
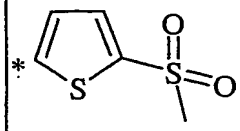
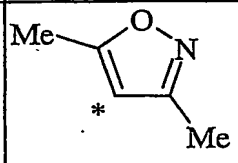
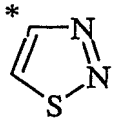
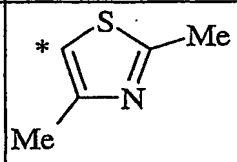
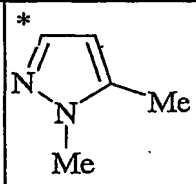
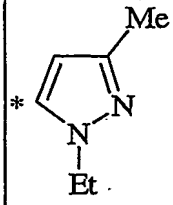
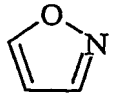
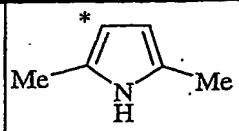
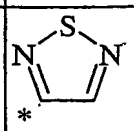
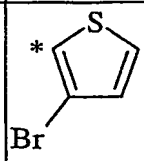
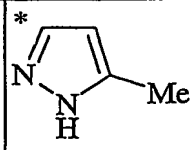
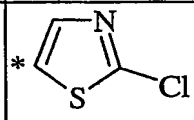
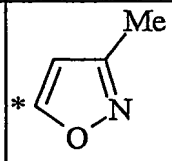
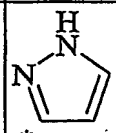
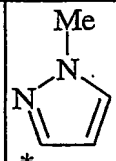
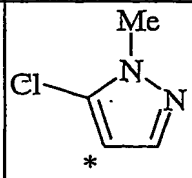
62		371
63		347
64		347
65		343
66		355
67		355
68		359
69		359

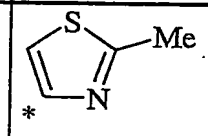
Ex	R^1	M/z
70		359
71		355
72		380
73		301
74		312
75		362
76		362
77		315
78		396
79		350

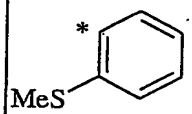
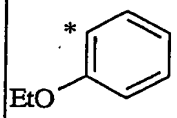
Ex	R^1	M/z
80		350
81		379
82		364
83		392
84		363
85		318
86		365
87		460
88		341
89		371

Ex	R^1	M/z
90		336
91		355
92		365
93		385
94		355
95		355
96		376
97		300
98		368
99		351

Ex	R^1	M/z
100		362
101		362
102		369
103		395
104		330
105		319
106		346
107		329
108		343
109		302

Ex	R^1	M/z
110		328
111		319
112		396
113		315
114		353
115		316
116		301
117		315
118		350

Ex	R^1	M/z
119		332

Ex	R^1	M/z
120		357
121		355

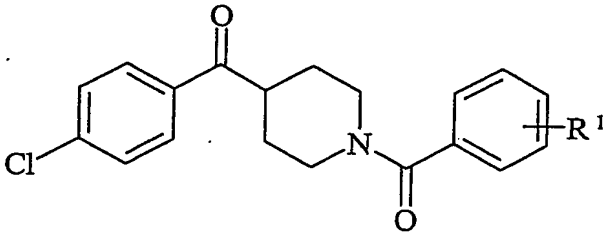
Example 122

1-(2-Cyanobenzoyl)-4-(4-chlorobenzoyl)piperidine

In a test tube was placed 2-cyanobenzoic acid (49mg, 0.33mmol), 4-(4-chlorobenzoyl)piperidine hydrochloride (86mg, 0.33mmol), N-methylmorpholine (36µl, 0.33mmol) and anhydrous THF (4ml). The resulting suspension was stirred at room temperature for 15minutes before the addition of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride hydrate (106mg, 0.36mmol). The reaction was left to stir overnight at room temperature then worked up. 1M HCl (2ml) was added and the reaction was capped and briefly shaken then allowed to settle. The organic layer was transferred to a 4 dram vial then evaporated to yield crude product. This material was purified by prep LCMS (1-40% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN) to yield a solid (19mg, 16%). m/z 353.

Examples 123-128

The procedure described in Example 122 was repeated using the appropriate reagent to replace the "2-cyanobenzoic acid" to obtain the compounds described below.



Ex	R^1	M/z
123 [1]	3-MeO	358
124	4- MeO	358
125	3-CN	353

Ex	R^1	M/z
126	2- MeO	358
127	4-CN	353
128	2,4,6-tri MeO	418

^{1} NMR: 1.60 (m, 2H), 1.90 (m, 2H), 3.20 (m, 2H), 3.70 9m, 1H), 3.80 (s, 3H), 4.10 (br s, 2H), 6.95 (m, 2H), 7.00 (d, 1H), 7.35 (t, 1H), 7.60 (d, 2H), 8.00 (d, 2H)

The following General Procedures were used to make Examples 129-193.

General Procedure XX

To the acid (A) in a 2-dram glass vial was added sequentially PS-DIEA (B) and a solution of HATU (C) in DMF (D). The mixture was agitated and allowed to stand for 5-10 minutes prior to the addition of a solution of 4-(4-fluorobenzoyl)piperidine hydrochloride (E) and DIEA (F) in DMF (G). The mixture was shaken, (sonicated if required to effect dissolution) and left to stand, without agitation for 16 h. The reaction mixture was poured onto an Isolute SCX-2 column (1 g, 0.4mmol/g) aligned over an Isolute-NH2 column (1 g, 0.6mmol/g) transferring with DCM (0.5ml). The columns were then eluted under atmospheric pressure with DCM (2.5 column volumes). The eluents were then evaporated *in vacuo*, taken up in MeCN (1ml), an LC-MS analysis sample taken (10ul) and evaporated again *in vacuo* to yield the final compound.

General Procedure YY

To the acid (A) in a 2-dram glass vial was added sequentially: PS-DIEA (B), a solution of 4-(4-fluorobenzoyl)piperidine hydrochloride (E) and DIEA (F) in DMF (G) and a solution of HATU (C) in DMF (D). The mixture was shaken, (sonicated if required to effect dissolution) and left to stand, without agitation for 16 hrs. The reaction mixture was filtered through a double fritted 6ml reservoir, the residue was washed with DCM (0.5ml) and the filtrated was concentrated *in vacuo*. The samples were purified by preparative HPLC. Preparative Reverse Phase HPLC was performed using an Xterra 19x50mm C18 column with a water (A) / acetonitrile (B) gradient at 25 ml/min as typified in the following table. The eluent was modified during chromatography with a flow of a 5% solution of ammonia in acetonitrile (C).

Time (mins)	A%	B%	C%
0	94	1	5
1	94	1	5
7.5	0 or 45	95 or 50	5
7.51	0	100	0

8.5	0	100	0
8.51	94	1	5
9.5	94	1	5

General Procedure ZZ

Procedure XX was observed except that the compounds were further dissolved in EtOAc, loaded onto an Isolute-Si 1g column and eluted with EtOAc (3 column volumes). A 15ul analysis sample (for LC-MS) was taken from the filtrate and the remaining evaporated *in vacuo* to provide the desired compounds.

General Procedure AA

Procedure YY was observed except that purification was performed using the Isco CombiFlash Optix-10 parallel flash chromatography system. The evaporated samples were dissolved in EtOAc (1ml) and loaded onto a 2g Isolute-Si column. These were attached to the Optics-10 system over a 12g silica column and run in one of the below methods:

i) Gradient of isohexane/EtOAc, Flow rate 30 ml/min
0 -3 minutes 50% - 100% EtOAc
3-6 minutes 100% EtOAc

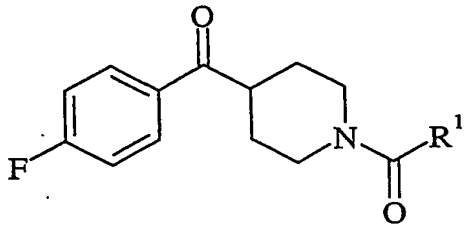
ii) Gradient of isohexane/EtOAc, Flow rate 30 ml/min
0 -5 minutes 100% EtOAc

Specific Variations of the above general Procedures are given in the following table

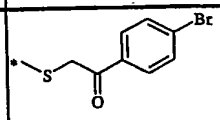
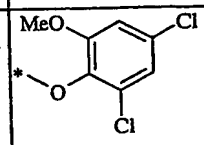
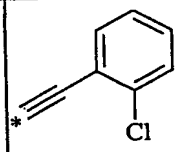
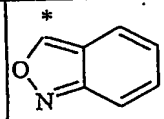
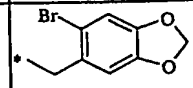
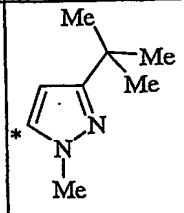
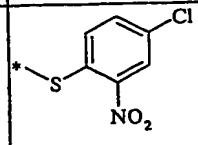
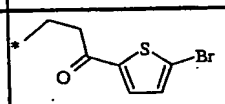
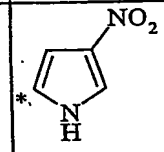
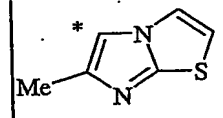
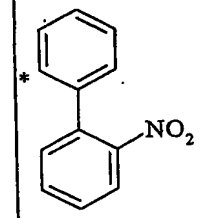
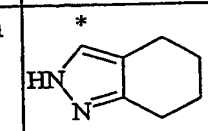
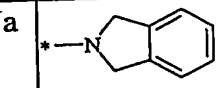
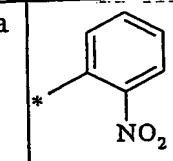
General Procedure	A (mmols)	B (mg) 3.56mmol/g	C (mmol)	D (ml)	E (mmol)	F (mmol)	G (ml)
XXa	0.225	220	0.25	2	0.25	0.5	0.66
XXb	0.225	220	0.25	1.5	0.25	0.25	1
XXc	0.225	220	0.25	1	0.25	0.388	1
XXd	0.225	220	0.25	2	0.25	0.25	0.6
YYa	0.225	220	0.25	1.5	0.25	0.25	1
ZZa	0.225	220	0.25	1	0.25	0.388	1

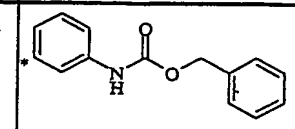
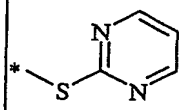
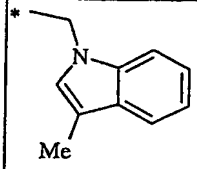
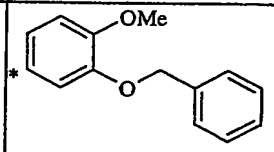
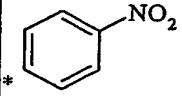
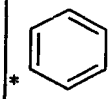
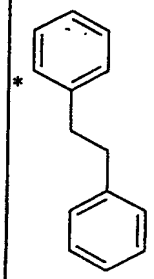
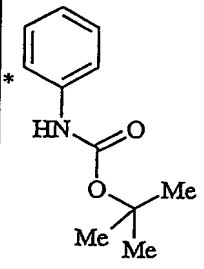
Examples 129-193

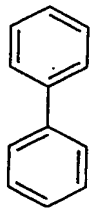
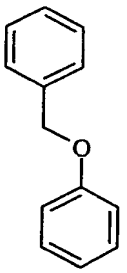
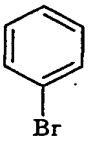
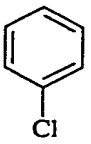
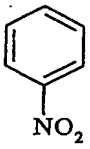
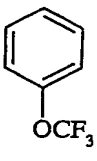
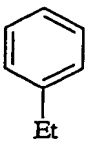
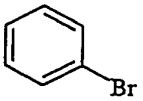
The following compounds were prepared by the General Procedures detailed above. "*" indicates the carbon atom that is attached to the carbonyl of formula (A).

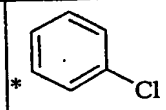
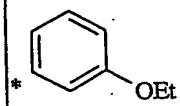
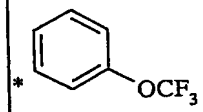
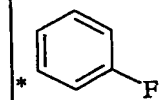
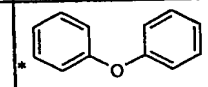
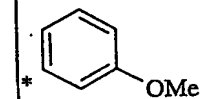
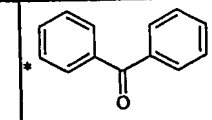
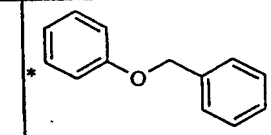
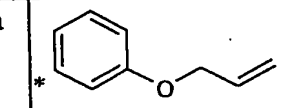
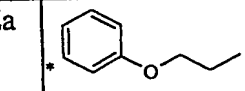
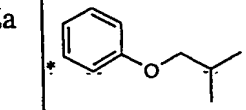
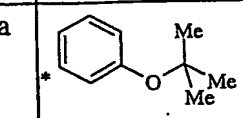


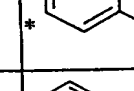
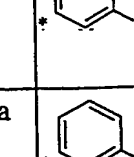
(A)

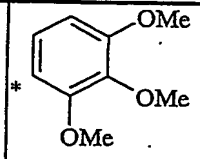
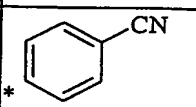
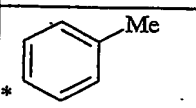
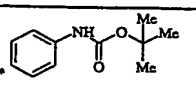
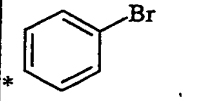
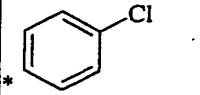
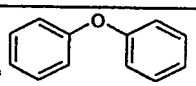
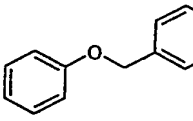
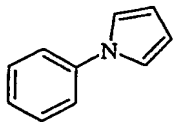
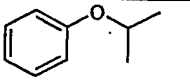
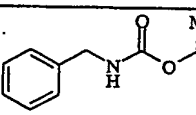
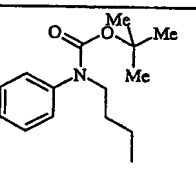
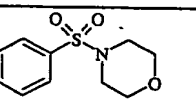
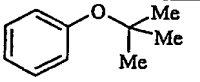
Ex	G. Proc	R^1	M/z
129	XXb		480.3
130	XXb		440.3
131	XXa		370.4
132	XXa		353.4
133	XXa		464.3
134	YYa		372.7
135	XXb		437.3
136	XXb		468.3
137	YYa		346.7
138	YYa		372.7
139	YYa		432.5
140	YYa		355
141	YYa		367.7
142	XXa		371.4

Ex	G. Proc	R^1	M/z
143	XXa		461.4
144	YYa		359
145	YYa		393.7
146	XXa		448.4
RE 3 [1]	XXd		357.36
147	XXc		312.45
148	XXc		416.48
149	XXc		427.46

Ex	G. Proc	R^1	M/z
150	XXc		388.47
151	XXc		418.45
152	XXc		390.35
153	XXc		346.42
154	XXc		347.45
155	XXc		396.42
156	XXc		340.5
157	ZZa		390.2

Ex	G. Proc	R^1	M/z
158	ZZa		346.3
159	ZZa		356.4
160	ZZa		396.3
161	ZZa		330.4
162	ZZa		404.3
163	ZZa		342.4
164	ZZa		416.3
165	ZZa		418.3
166	ZZa		368.4
167	ZZa		370.4
168	ZZa		384.4
169	ZZa		384.4

Ex	G. Proc	R^1	M/z
170	XXc		304.52
171	XXc		419.55
172	XXc	*i*-Pr	278.51
173	XXc	Hept-3-yl	334.4
174	XXc	*t*-Butyl	292.4
175	XXc		306.51
176	XXc		370.52
177	XXc	Pent-3-yl	306.55
178	XXc		306.52
179	XXc		419.57
180	XXc		421.54
181	XXc		320.54
182	XXc		354.55
183	XXc		337.45

Ex	G. Proc	R^1	M/z
184	XXc		402.54
185	ZZa		337.3
186	ZZa		326.3
187	ZZa		427.3
188	ZZa		390.2
189	ZZa		346.3
190	ZZa		404.3
191	ZZa		418.3
192	ZZa		377.3
193	ZZa		370.4
194	ZZa		441.3
195	ZZa		427.3
196	ZZa		461.3
197	ZZa		384.4

[1] NMR (300MHz) 1.8-2.2 (4H), 3.0-3.4 (2H), 3.4-4.0 (2H), 4.5-4.8 (1H), 7.2 (2H), 7.6 (2H), 8.0 (2H), 8.4 (2H).

Example 198

1-(4-Methoxybenzoyl)-4-(4-fluorobenzoyl)piperidine

To paramethoxy benzoic acid (34mg, 0.225mmol) in a 2-dram glass vial was added a suspension of 4-(4-fluorobenzoyl)piperidine hydrochloride (0.25mmol (60mg), HATU (0.25mmol, 95mg) and DIEA (0.75mmol, 130ul) in THF (2ml), transferring with a further 1 ml of THF. The mixture was stirred for 19h, filtered over Isolute SCX-2 (2x2g) washing through with THF (1 column volume). The filtrate in turn was filtered over Isolute-NH2 (1g) washing with THF (1 column volume). The filtrates were evaporated in vacuo to result a colourless oil. Dissolution and evaporation from methanol yielded a white solid. Yield

64.6mg, 76.8% M+H+ 342.47. NMR (300MHz) 1.8-2.0 (4H), 3.0-3.2 (2H), 3.4-3.6 (1H), 3.9 (3H), 4-4.6 (2H), 6.9 (2H), 7.2 (2H), 7.4 (2H), 8.0 (2H).

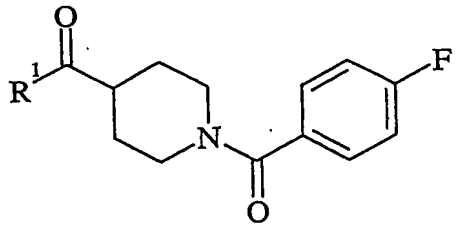
Example 199

1-(4-Fluorobenzoyl)-4-(3-chlorobenzoyl)piperidine

To a stirred solution of 1-(4-fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl) piperidine (Method 2; 327mg, 1.11mmol) in anhydrous THF (8ml) at 0°C was added a 0.5M solution of 3-chlorophenyl magnesium bromide in THF (6.66ml, 3.33mmol). The reaction was stirred at 0°C for ten minutes then allowed to warm to room temperature and stirred for a further 30 minutes. The reaction was quenched with sat NH_4Cl (~20ml) and extracted with EtOAc (2 x 15ml). The combined organic layers were washed with brine then dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (10g Silica, 20% EtOAc/isohexane to 40%EtOAc/isohexane) to yield a solid (55mg, 15%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.85 (m, 2H), 3.20 (t, 2H), 3.70 (m, 1H), 4.00 (m, 2H), 7.20 (t, 2H), 7.40 (m, 2H), 7.50 (t, 1H), 7.65 (m, 1H), 7.90 (m, 2H); m/z 346.

Examples 196-205

The procedure described in Example 199 was repeated using the appropriate reagent to replace the "3-chlorophenyl magnesium bromide" to obtain the compounds described below.



Ex	R^1	NMR	M/z
200	Benzyl	NMR (DMSO-d_6): 1.45 (m, 2H), 1.85 (br s, 2H), 2.80 (m, 1H), 2.95 (br s, 2H), 3.85 (s, 2H), 7.15 (d, 2H), 7.30 (m, 5H), 7.45 (m, 2H)	326
201	4-Propyl-phenyl	NMR (DMSO-d_6): 0.90 (t, 3H), 1.60 (m, 4H), 1.85 (m, 2H), 2.65 (t, 2H), 3.20 (t, 2H), 3.70 (m, 1H), 4.00 (m, 2H), 7.20 (t, 3H), 7.40 (d, 2H), 7.45 (m, 2H), 7.90 (d, 2H)	354

Ex	R^1	NMR	M/z
202	2-Chloro-thien-5-yl	NMR (DMSO-d_6): 1.65 (m, 2H), 1.85 (m, 2H), 2.20 (t, 2H), 3.55 (m, 1H), 4.05 (m, 2H), 7.20 (m, 3H), 7.45 (m, 2H), 7.90 (d, 1H)	352
203 [1]	2-Methyl-pyrid-6-yl		327
204	3-Methyl-phenyl	1.60 (m, 2H), 1.85 (br d, 2H), 2.40 (s, 3H), 3.20 (t, 2H), 3.70 (m, 1H), 4.00 (br d, 2H), 7.20 (t, 2H), 7.45 (m, 4H), 7.80 (m, 2H)	326
205	4-*t*-Butyl-Phenyl	1.30 (s, 9H), 1.60 (m, 2H), 1.80 (m, 2H), 3.20 (m, 2H), 3.70 (m, 1H), 4.00 (m, 2H), 7.20 (t, 2H), 7.45 (m, 2H), 7.55 (d, 2H), 7.90 (d, 2H)	368
206	3-Methoxy-phenyl	1.65 (m, 2H), 1.90 (m, 2H), 3.20 (m, 2H), 3.70 (m, 1H), 3.85 (s, 3H), 4.05 (m, 2H), 7.25 (m, 3H), 7.45 (m, 4H), 7.60 (d, 1H)	342
207	4-Phenyl-phenyl	1.60 (m, 2H), 1.90 (m, 2H), 3.20 (t, 2H), 3.75 (m, 1H), 4.05 (br d, 2H), 7.20 (t, 2H), 7.45 (m, 5H), 7.70 (d, 2H), 7.80 (d, 2H), 8.05 (d, 2H)	388
208 [2]	Cyclopentyl		304
209	1,3-Benzodioxol-5-yl		356

[1] Further purified by prep LCMS (1-40% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN)

[2] Further purified by prep LCMS (9-95% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN)

Example 210

1,4-Bis-(4-fluorobenzoyl)-4-methylpiperidine

To a stirred solution of 1,4-bis-(4-fluorobenzoyl)piperidine (Example 8; 200mg, 0.61mmol) in anhyd THF (5ml) was added a 1M solution of lithium bis(trimethyl)amide in THF (1.53ml, 1.53mmol). The reaction was stirred at room temperature for 15 minutes before the addition of MeI (346mg, 2.44mmols). The reaction was then left to stir overnight at room temperature. Water (2ml) was added to the reaction then the volatiles were removed under reduced pressure. The product was partitioned between 1M HCl (15ml) and DCM (20ml).

The organic layer was then separated and washed with sat $NaHCO_3$ (15ml) and brine (10ml) then dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (10g Silica, 10% EtOAc/isohexane to 40% EtOAc/isohexane) to yield a solid (83mg, 39%). NMR (DMSO-d_6): 1.40 (s, 3H), 1.65 (m, 2H), 2.10 (m, 2H), 3.35 (m, 2H), 3.60 (m, 2H), 7.25 (m, 4H), 7.45 (m, 2H), 7.80 (m, 2H); m/z 344.

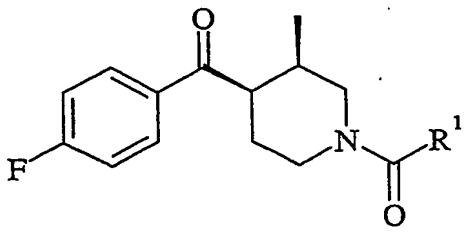
Example 211

3,4-Cis-1,4-Bis-(4-fluorobenzoyl)-3-methylpiperidine

To a stirred solution of 3-methyl-4-(4-fluorobenzoyl)piperidine hydrochloride (Method 4; 119mg, 0.46mmol) and triethylamine (140mg, 1.39mmol) in DCM (4ml) was added 4-fluorobenzoyl chloride (66mg, 0.41mmol). The reaction was stirred at room temperature for 30 minutes then worked up. Reaction transferred to a separating funnel, diluted to 10ml with DCM then washed with 1M HCl (2 x 5ml), sat $NaHCO_3$ (5ml) and brine (5ml). The organic layer was then dried ($MgSO_4$), filtered and evaporated to yield a solid (101mg, 71%). NMR (DMSO-d_6): 0.70 (d, 3H), 1.60 (m, 1H), 1.95 (m, 1H), 2.25 (m, 1H), 3.20 (m, 1H), 3.40 (m, 1H), 3.80 (m, 2H), 3.95 (br m, 1H), 7.25 (t, 2H), 7.30 (t, 2H), 7.45 (m, 2H), 8.05 (m, 2H); m/z 344.

Examples 212-213

The procedure described in Example 211 was repeated using the appropriate reagent to replace the "4-fluorobenzoyl chloride" to obtain the compounds described below (wherein the stereochemistry depicted in the below formula is relative rather than absolute, i.e. the compounds are the cis isomers).



Ex	R^1	NMR	M/z
212	Cyclopropyl	NMR (DMSO-d_6): 0.70 (m, 7H), 1.60 (m, 1H), 1.90 (m, 2H), 2.20 (m, 1H), 3.10 (br m, 1H), 3.40 (br d, 1H), 3.80 (m, 1H), 4.05 (m, 1H), 4.25 (m, 1H), 7.30 (t, 2H), 8.00 (m, 2H)	290
213	Thien-2-yl	NMR (DMSO-d_6): 0.70 (d, 3H), 1.65 (m, 1H), 1.95 (m, 1H), 2.30 (m, 1H), 3.30 (m, 1H), 3.50 (m, 1H), 3.90 (m, 1H), 4.10 (m, 1H), 4.20 (m, 1H), 7.10 (m, 1H), 7.30 (t, 2H), 7.35 (m, 1H), 7.70 (m, 1H), 8.10 (m, 2H)	332

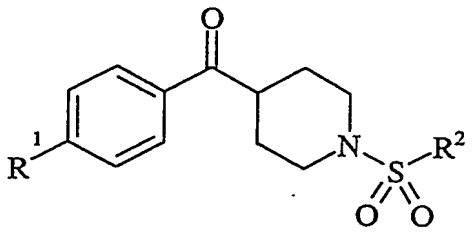
Example 214

1-(Thien-2-ylsulphonyl)-4-(4-chlorobenzoyl)piperidine

To a stirred solution of (4-chlorophenyl)(4-piperidyl)methanone hydrochloride (100mg, 0.41mmol) and triethylamine (104mg, 1.03 mmol) in DCM (4ml) was added 2-thiophenesulphonyl chloride (71mg, 039mmol). The reaction was stirred at room temperature for 1 hour then diluted to approximately 10ml with DCM and transferred to a sep funnel. The solution was then washed with 2M HCl (5ml), water (5ml) and brine (5ml), then dried, filtered and evaporated to yield the product as a solid (83mg, 55%). NMR (DMSO-d_6): 1.55 (m, 2H), 1.90 (d, 2H), 2.55 (m, 2H), 3.50 (m, 1H), 3.65 (d, 2H), 7.30 (s, 1H), 7.50 (d, 2H), 7.60 (br s, 1H), 8.00 (d, 2H), 8.05 (m, 1H); m/z 370.

Examples 215-232

The procedure described in Example 12 was repeated using the appropriate reagent to replace the "2-thiophenesulphonyl chloride" to obtain the compounds described below. In some cases a base wash was also carried out ($NaHCO_3$) prior to washing with brine.



Ex	R^1	R^2	NMR	M/z
215	F	2-CF_3 phenyl		416
216	F	2-Br phenyl		426

217	F	3-Br phenyl	(DMSO-d_6): 1.55 (m, 2H), 1.85 (br d, 2H), 3.45 (t, 1H), 3.70 (br d, 2H), 7.30 (t, 2H), 7.60 (t, 1H), 7.80 (d, 1H), 7.90 (s, 1H), 7.95 (d, 1H), 8.00 (m, 2H)	426
218	F	3-CF_3 phenyl		416
219	F	4-Cl phenyl		382
220	F	2-Cl, 4-CN phenyl		407
2212	F	3-Cl, 4-NH_2 phenyl	(DMSO-d_6): 1.55 (m, 2H), 1.85 (d, 2H), 2.40 (m, 2H), 3.45 (m, 1H), 3.60 (d, 2H), 6.30 (s, 2H), 6.90 (d, 1H), 7.30 (t, 2H), 7.40 (d, 1H), 7.50 (s, 1H), 8.00 (m, 2H)	397
222	F	4-MeO phenyl		378
2231	F	4-F benzyl	1.45 (m, 2H), 1.80 (d, 2H), 2.90 (t, 2H), 3.55 (m, 3H), 4.40 (s, 2H), 7.20 (t, 2H), 7.35 (t, 2H), 7.45 (m, 2H), 8.05 (m, 2H)	
224	Me	4-F phenyl		362
225	F	4-F phenyl		366
226	MeO	4-F phenyl		378
227	Cl	4-F phenyl	1.90 (m, 4H), 2.60 (m, 2H), 3.20 (m, 1H), 3.75 (m, 2H), 7.25 (m, 2H), 7.40 (d, 2H), 7.80 (m, 4H)	
228	Cl	Iso propyl	1.35 (d, 6H), 1.90 (m, 4H), 3.25 (m, 3H), 3.40 (m, 1H), 3.85 (m, 2H), 7.45 (d, 2H), 7.85 (d, 2H)	330
229	Cl	Benzyl	1.80 (br m, 4H), 2.85 (m, 2H), 3.25 (m, 1H), 3.60 (m, 2H), 4.25 (s, 2H), 7.40 (br m, 7H), 7.85 (d, 2H)	
230	Cl	4-Me phenyl	1.90 (m, 4H), 2.45 (s, 3H), 2.55 (m, 2H), 3.10 (m, 1H), 3.80 (m, 2H), 7.35 (d, 2H), 7.40 (d, 2H), 7.65 (d, 2H), 7.80 (d, 2H)	378
231	Cl	Me	2.00 (m, 4H), 2.85 (s, 3H), 3.00 (m, 2H), 3.35 (m, 1H), 3.80 (m, 2H), 7.45 (d, 2H), 7.85 (d, 2H)	302
232	MeO	4-Me phenyl	1.90 (m, 4H), 2.45 (s, 3H), 2.55 (m, 2H), 3.15 (m, 1H), 3.75 (m, 2H), 3.85 (s, 3H), 6.90 (d, 2H), 7.35 (d, 2H), 7.65 (d, 2H), 7.85 (d, 2H)	374

[1] Product purified by column chromatography (10g Silica, 40% EtOAc/isohexane) to yield white solid.

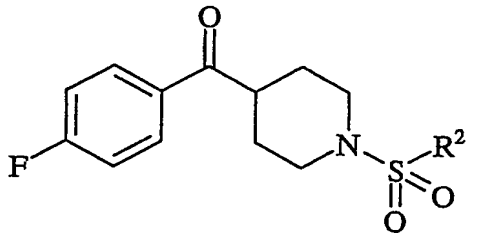
[2] The sulphonylchloride used was 4-acetamido-3-chlorobenzenesulfonyl chloride, the acetyl group was removed during the reaction/work up.

Example 233

1-(3-Chlorophenylsulphonyl)-4-(4-fluorobenzoyl)piperidine

To a stirred solution of 4-(4-fluorbenzoyl)piperidine hydrochloride (51mg, 0.21mmol) and triethylamine (52mg, 0.51 mmol) in DCM (8ml) was added 3-chlorobenzenesulfonyl chloride (40mgs, 0.19m.mol) The reaction was stirred at room temperature for 16 hours. The solution was then washed with 2M HCl (5ml), saturated sodium carbonate (5ml) and water (5ml) using a Mettler Toledeo Myriad ALLEX liquid –liquid extractor then dried, filtered and evaporated to yield the product as a solid (58.8mgs, 62.4%). M/z 382.

Examples 234-262



Ex	R^2	M/z
234	2,5-Dimethylphenyl	375
235	2-Chloro-6-methylphenyl	396
236	5-Fluoro-2-methylphenyl	379
237	2-Methylphenyl	361
238	2-Chlorophenyl	382
239	2,5-Dichlorothien-3-yl	422
240	2-Fluorophenyl	365
241	2,4,5-Trifluorophenyl	401
242	3-Fluorophenyl	365
243	3,5-Dimethylisoxazol-4-yl	366
244	2-Cyanophenyl	372

Ex	R^2	M/z
245	2-Nitro-4-methoxyphenyl	422
246	4-Ethylphenyl	375
247	2-Chloro-4-flurophenyl	400
248	2-Methoxy-5-methylphenyl	391
249	3-Methoxyphenyl	377
250	2,4-Difluorophenyl	383
251	Thien-3-yl	353
252	3-Methylphenyl	361
253	5-Chloro-1,3-dimethylpyrazol-4-yl	400
254	1-Butyl	327

Ex	R^2	M/z
255	4-Bromophenyl	426
256	Isopropyl	313
257	4-Methylphenyl	361
258	4-Trifluoromethylphenyl	415

Ex	R^2	M/z
259	4-Acetamidophenyl	404
260	2-Chlorothien-5-yl	388
261	2,6-Diflurophenyl	383
262	Ethyl	299

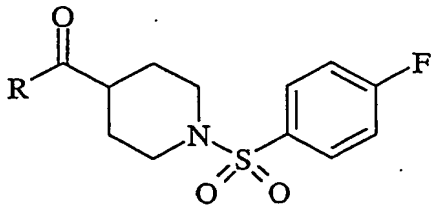
Example 263

1-(4-Fluorophenylsulphonyl)-4-(3-methoxybenzoyl)piperidine

To a stirred solution of 1-(4-fluorophenylsulphonyl)-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine (Method 8; 250mg, 0.76mmol) in anhydrous THF (5ml) at 0°C was added a 1M solution of 3-methoxyphenylmagnesium bromide in THF (2.66ml, 2.66mmol). The reaction was stirred at 0°C for ten minutes then allowed to warm temperature and stirred for a further 30 minutes. The reaction was quenched with sat NH_4Cl solution then extracted with EtOAc (2x15ml). The organic layers were combined, washed with brine (10ml), dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (10g Silica, 20% EtOAc/isohexane to 40% EtOAc/isohexane) to yield a white solid (115mg, 40%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 2.70 (m, 2H), 3.50 (m, 1H), 3.70 (m, 2H), 3.85 (s, 3H), 7.20 (m, 1H), 7.50 (m, 5H), 7.85 (m, 2H); m/z 378.

Examples 264-270

The procedure described in Example 263 was repeated using the appropriate reagent to replace the "3-methoxyphenylmagnesium bromide" to obtain the compounds described below.



Ex	R	NMR	M/z
264	3-Me phenyl	(DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 2.40 (s, 3H), 2.70 (t, 2H), 3.45 (m, 1H), 3.70 (m, 2H), 7.45 (m, 4H), 7.70 (m, 2H), 7.90 (m, 2H)	362

Ex	R	NMR	M/z
265 [1]	2-Me phenyl	(DMSO-d_6): 1.60 (m, 2H), 1.85 (m, 2H), 2.30 (s, 3H), 2.65 (m, 2H), 3.20 (m, 1H), 3.60 (m, 2H), 7.25 (m, 2H), 7.35 (m, 1H), 7.40 (m, 2H), 7.55 (d, 1H), 7.80 (m, 2H)	362
266	2- MeO phenyl	(DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 2.65 (m, 2H), 3.20 (m, 1H), 3.65 (m, 2H), 3.80 (s, 3H), 7.00 (t, 1H), 7.15 (d, 1H), 7.45 (m, 4H), 7.80 (m, 2H)	378
267	3,5-di F phenyl	1.50 (m, 2H), 1.85 (br d, 2H), 2.45 (m, 2H), 3.45 (m, 1H), 3.65 (d, 2H), 7.50 (m, 3H), 7.65 (m, 2H), 7.85 (m, 2H)	384
268 [3]	2,4-di F Benzyl	1.50 (m, 2H), 1.95 (m, 2H), 2.35 (m, 2H), 2.55 (m, 1H), 3.60 (d, 2H), 3.85 (s, 2H), 7.00 (m, 1H), 7.15 (m, 1H), 7.25 (m, 1H), 7.50 (t, 3H), 7.85 m, 2H)	398
269 [2]	2-Me, 4-F phenyl	1.55 (m, 2H), 1.85 (m, 2H), 2.30 (s, 3H), 2.60 (m, 2H), 3.20 (m, 1H), 3.65 (m, 2H), 7.10 (m, 2H), 7.40 (t, 2H), 7.70 (m, 1H), 7.85 (m, 2H)	380
270 [2]	2,4-di Me phenyl	1.55 (m, 2H), 1.85 (m, 2H), 2.30 (d, 6H), 2.65 (m, 2H), 3.20 (m, 1H), 3.60 (m, 2H), 7.05 (m, 2H), 7.40 (t, 2H), 7.50 (d, 1H), 7.85 (m, 2H)	376

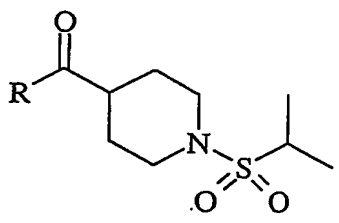
[1] The material recovered from the initial chromatography was purified by prep LCMS (1-40% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN).

[2] The material recovered from the initial chromatography was purified by prep LCMS (5-95% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN).

[3] The product was purified by an EtOAc recrystallization.

Examples 271-2

The procedure described in Example 263 was repeated using the appropriate reagent to replace the "3-methoxyphenylmagnesium bromide" and 1-(isopropylsulphonyl)-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine (Method 9) to obtain the compounds described below.



Ex	R	NMR	M/z
271	3,5-di F phenyl	(DMSO-d_6): 1.20 (d, 6H), 1.50 (m, 2H), 1.85 (br d, 2H), 3.05 (t, 2H), 3.30 (m, 1H), 3.65 (m, 3H), 7.55 (m, 1H), 7.65 (m, 2H)	332
272	2,4 di F benzyl	1.20 (d, 6H), 1.45 (m, 2H), 1.90 (br d, 2H), 2.70 (m, 1H), 2.95 (t, 2H), 3.30 (m, 2H), 3.65 (br d, 2H), 3.90 (s, 2H), 7.00 (m, 1H), 7.15 (m, 1H), 7.25 (m, 1H)	346

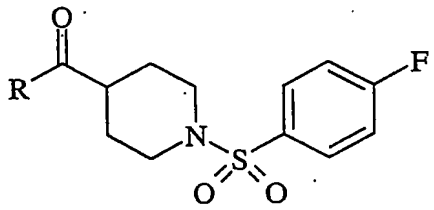
Example 273

1-(4-Fluorophenylsulphonyl)-4-(3-fluorobenzoyl)piperidine

To a stirred solution of 1-(4-fluorophenylsulphonyl)-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine (Method 8; 36mg, 0.11mmol) in anhydrous THF (1ml) was added a 0.5M solution of 3-flurophenyl magnesium bromide in THF (0.78ml, 0.39mmol). The reaction was stirred at room temperature for 3 hours then quenched with sat NH_4Cl solution. Water (1ml) and EtOAc (3ml) were added and the reaction was capped and briefly shaken then allowed to settle. The organic layer was transferred to a weighed vial then evaporated to yield crude product. This was purified by prep LCMS to yield a gum (9mg, 20%). M/z 366.

Examples 274-280

The procedure described in Example 273 was repeated using the appropriate reagent to replace the "3-flurophenyl magnesium bromide" to obtain the compounds described below.



Ex	R	M/z
274	4-*t*-Butylphenyl	404
275	1,3-Benzodioxol-5-yl	392
276	6-Methylpyrid-2-yl	363
277 [1]	4-propyphenyl	390

Ex	R	M/z
278	5-Chlorothie-2-yl	388
279	Pyrid-2-yl	349
280	Thien-2-yl	354

[1] NMR: (DMSO-d_6): 0.85 (t, 3H), 1.55 (m, 4H), 1.80 (br d, 2H), 2.60 (t, 2H), 3.40 (m, 1H), 3.65 (m, 2H), 7.30 (d, 2H), 7.50 (t, 2H), 7.85 (m, 4H)

Example 281

1-(4-Fluorophenylsulphonyl)-4-(4-fluorobenzoyl)-4-ethylpiperidine

To a stirred solution of 1-(4-fluorophenylsulphonyl)-4-(4-fluorobenzoyl)piperidine (Example 225; 200mg, 0.55mmol) in anhydrous THF (5ml) at 0°C was added a 1M solution of lithium bis(trimethyl)amide in THF (1.1ml, 1.1mmol). The reaction was allowed to stir briefly before the addition of ethyl iodide (171mg, 1.1mmol). The reaction was then allowed to warm to room temperature and left to stir overnight. The volatiles were removed under reduced pressure and the resulting gummy solid was partitioned between water and EtOAc. The organic layer was separated then washed with brine, dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (20g Silica, 10% EtOAc/isohexane to 40% EtOAc/isohexane) to yield a white solid (16mg, 7%). NMR (DMSO-d_6): 0.70 (t, 3H), 1.65 (m, 2H), 1.85 (q, 2H), 2.25 (br d, 2H), 2.40 (m, 2H), 3.35 (m, 2H), 7.25 (t, 2H), 7.50 (t, 2H), 7.70 (m, 2H), 7.80 (m, 2H); m/z 394.

Example 282

1-(Thien-2-ylmethyl)-4-(4-chlorobenzoyl)piperidine

To a stirred suspension of (4-chlorophenyl)(4-piperidyl)methanone hydrochloride (200mg, 0.82mmol) in THF (6ml) was added 2-thiophene carboxaldehyde (101mg, 0.90mmol). The reaction was stirred at 35°C for 5 hours before the addition of sodium triacetoxyborohydride (434mg, 2.05mmol). The reaction was left to stir at 35°C for 48 hours before quenching by the addition of water (10ml). Volatiles removed under reduced pressure and the resulting solid was partitioned between water and DCM. The DCM layer was separated off and the aqueous was reextracted with DCM. The organic phases were combined and washed with brine, then dried, filtered and evaporated to yield crude product. This crude product was dissolved in DCM and treated with PS-trisamine (60mg) and PS-tosylchloride (290mg) for 12 hours. The polymer bound reagents were filtered off and the solvent was removed to yield the product (98mg, 38%). NMR: 1.85 (m, 4H), 2.00 (m, 2H), 3.00 (m, 2H), 3.20 (m, 1H), 3.75 (s, 2H), 6.95 (m, 2H), 7.25 (m, 1H), 7.40 (d, 2H), 7.85 (d, 2H).

Example 283

1-(Benzyl)-4-(4-bromobenzoyl)piperidine

To a stirred solution of ethyl-N-benzyl isonipecotate (5.7g, 24.2mmol) in methanol (60ml) was added a 1M solution of NaOH (60ml, 60mmol). The resulting mixture was stirred for 4 hours. The solution was neutralised by the addition of 2M HCl solution (30ml, 60mmol) then the solvent was removed *in vacuo*. The residue was triturated with THF (3x100ml), the triturates were combined and evaporated to give 4.12g of N-benzylisonipecotic acid which was used without further purification. The N-benzylisonipecotic acid (3.94g, 18.0mmol) was suspended in THF (100ml) under Argon then cooled to –78°C. A 2M solution of lithium diisopropylamide was then added dropwise with stirring (22.5ml, 45mmol). The reaction was then allowed to warm to room temperature followed by refluxing under argon for a further hour (oil bath temperature 50°C). This solution was then allowed to cool back to room temperature. In a separate flask 4-bromobenzoyl chloride (5.93g, 27mmol) was dissolved in THF (100ml) and cooled to –78°C. The dianion solution was added dropwise to the acid chloride solution over 30 minutes. The reaction mixture was stirred at –78°C for a further 30 minutes then allowed to warm to room temperature over night. The reaction was quenched by the addition of 2M HCl (36ml, 72mmol) in 100g of crushed ice. The product was extracted with 3x200ml DCM, dried over $MgSO_4$ and then evaporated to give a brown oil. Flash column chromatography was performed, eluting with 0 to 5% MeOH in DCM. 1.7g of pure material was obtained as an orange solid. M/z 358.

Example 284

1-(Pyrimidin-2-yl)-4-(4-fluorobenzoyl)piperidine

A solution of 4-(4-flurobenzoyl)piperidine hydrochloride (300mg, 1.23mmol), 2-chloropyrimidine (141mg, 1.23mmol) and triethylamine (261mg, 2.58mmol) in EtOH (10ml) was stirred at reflux for 5 hours. The reaction was then cooled to room temperature and the solvent was removed under reduced pressure. The crude product was partitioned between EtOAc (20ml) and water (20ml). The organic layer was separated, washed with brine (10ml) then dried ($MgSO_4$), filtered and evaporated to yield crude product. This material was purified by column chromatography (DCM eluent) to yield the product as an oil which crystallised on standing (123mg, 35%). NMR (DMSO-d_6): 1.50 (m, 2H), 1.83 (br d, 2H), 3.10 (m, 2H), 3.75 (m, 1H), 4.65 (br d, 2H), 6.60 (t, 1H), 7.35 (t, 2H), 8.10 (m, 2H), 8.30 (d, 2H); m/z 286.

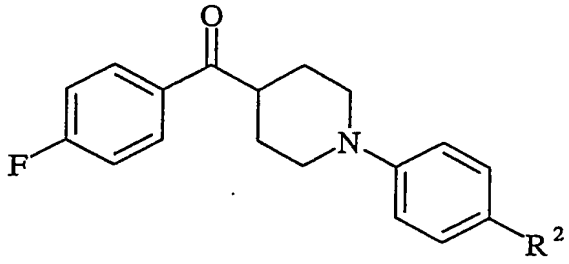
Example 285

1-(4-Trifluoromethylphenyl)-4-(4-fluorobenzoyl)piperidine

Copper iodide (10mg, 0.05mmol), K_3PO_4 (636mg, 3mmol) and 4-(4-fluorobenzoyl)piperidine hydrochloride (292mg, 1.2mmol) were put into a glass tube. The tube was sealed with a subaseal and evacuated and back filled with Argon. This Argon purge was repeated three times. Isopropanol (1ml), ethylene glycol (111µl) and 4-iodobenzotrifluoride (272mg, 1mmol) were then added by syringe. The reaction was warmed to 75°C and left to stir at this temperature over night. The reaction was cooled to room temperature and partitioned between water (10ml) and ether (15ml). The layers were separated and the aqueous layer was reextracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (10g Silica, eluting with 10% EtOAc/isohexane to 40% EtOAc/isohexane) to yield a solid (54mg, 15%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.85 (br d, 2H), 3.00 (t, 2H), 3.70 (m, 1H), 3.90 (br d, 2H), 7.05 (d, 2H), 7.35 (t, 2H), 7.45 (d, 2H), 8.10 (m, 2H); m/z 352.

Examples 286-289

The procedure described in Example 285 was repeated using the appropriate reagent to replace the "4-iodobenzotrifluoride" to obtain the compounds described below. In cases where the "iodo" compound was a solid it was added at the start of the reaction prior to the Argon purge.



Ex	R^2	NMR	M/z
286	MeO	(DMSO-d_6): 1.75 (m, 2H), 1.90 (br d, 2H), 2.85 (m, 2H), 3.55 (m, 3H), 3.70 (s, 3H), 6.80 (d, 2H), 6.90 (d, 2H), 7.30 (t, 2H), 8.05 (m, 2H)	314

Ex	R^2	NMR	M/z
287	MeC(O)NH-	(DMSO-d_6): 1.65 (m, 2H), 1.85 (br d, 2H), 2.00 (s, 3H), 2.80 (m, 2H), 3.55 (m, 1H), 1.60 (br d, 2H), 6.85 (d, 2H), 7.40 (m, 4H), 8.10 (m, 2H), 9.65 (s, 1)	341
288	F	(DMSO-d_6): 1.65 (m, 2H), 1.85 (br d, 2H), 2.80 (m, 2H), 3.55 (m, 1H), 3.60 (br d, 2H), 6.95 (m, 2H), 7.00 (t, 2H), 7.35 (t, 2H), 8.10 (m, 2H)	302
289	MeC(O)-	(DMSO-d_6): 1.60 (m, 2H), 1.85 (br d, 2H), 2.40 (s, 3H), 3.10 (m, 2H), 3.70 (m, 1H), 4.00 (br d, 2H), 7.00 (d, 2H), 7.35 (t, 2H), 7.80 (d, 2H), 8.10 (m, 2H)	326

Example 290

1-(Pyrid-4-yl)-4-(4-methoxybenzoyl)piperidine

To a stirred suspension of 1-(pyrid-4-yl)-4-(carboxy)piperidine (10.31 g, 50 mmol) in DCM (200 ml) at 4°C, was added oxalyl chloride (13 ml, 151.3 mmol) and DMF (cat). The mixture was allowed to warm to ambient temperature and stirred for 18 hours. Volatile material was removed by evaporation to give a solid. This solid was added slowly to a stirred mixture of aluminium chloride (40.0 g, 300 mmol) and anisole (40 ml, 368 mmol). The mixture was heated to 85°C and stirred for 3 hours, then allowed to cool to ambient temperature and stirred for a further 16 hours. The mixture was poured onto an ice/water mix. This was extracted with DCM (400 ml). The extract was washed with water (150 ml), brine (50 ml), water (2 x 200 ml) and dried over $MgSO_4$. Volatile material was removed by evaporation to leave a solid, which was purified by flash chromatography, eluting with 5-10% methanol in DCM to give a solid. This was recrystallized from ethanol to give the title compound (0.839 g) a solid. NMR (d_6-DMSO): 1.55 (m, 2H), 1.78 (m, 2H), 3.00 (t, 2H), 3.68 (m, 1H), 3.83 (s, 3H), 3.94 (m, 2H), 6.80 (d, 2H), 7.03 (d, 2H), 7.98 (d, 2H), 8.10 (d, 2H), MS: (ESP^+) m/z 297.0.

Example 291

1-(6-Chloronaphth-2-ylmethyl)-4-(4-fluorobenzoyl)piperidine

A solution containing 2-chloro-6-chloromethylnaphthalene (European Journal of Medicinal Chemistry (1984), 19(3), 205-14; 0.11g; 0.5mmol) in DMF (3ml) was added to 4-(4-fluorobenzoyl)piperidine hydrochloride (weighed at 0.5mmol) in DMF (3ml). Solid

potassium carbonate was added and the mixture stirred at 100°C for 3 hours. After cooling, the mixture was evaporated to approx. 1 ml and water (7ml) was added. The solid products were collected by filtration and washed with water (1ml). Yield 90%. M/z 382.2.

Example 292

1-(4-Fluoroanilinothiocarbonyl)-4-(4-fluorobenzoyl)piperidine

To a stirred solution of 4-(4-fluorobenzoyl)piperidine hydrochloride (300mg, 1.22mmol) and triethylamine (134mg, 1.32mmol) in DCM (6ml) was added 4-fluorophenyl isothiocyanate (170mg, 1.1mmol). The reaction was left to stir at room temperature for 15 minutes then worked up. The reaction was transferred to a separating funnel and diluted to approximately 5ml with DCM. The DCM was washed with 1M HCl (10ml), water (10ml) and brine (5ml) then dried ($MgSO_4$), filtered and evaporated to yield a solid (300mg, 68%). NMR (DMSO-d_6): 1.50 (m, 2H), 1.85 (br d, 2H), 3.30 (t, 2H), 3.70 (m, 1H), 4.75 (br d, 2H), 7.10 (t, 2H), 7.30 (m, 2H), 7.35 (t, 2H), 8.10 (m, 2H), 9.25 (s, 1H); m/z 361.

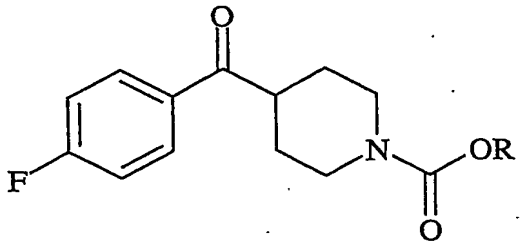
Example 293

1-(Phenoxycarbonyl)-4-(4-fluorobenzoyl)piperidine

To a stirred suspension of 4-(4-fluorobenzoyl)piperidine hydrochloride (244mg, 1mmol) in DCM (10ml) was added PS-DIEA, 3.66mmol/g, 683mg. The reaction was stirred for 15 minutes, then phenyl chloroformate (188mg, 1.2mmol) was added. The reaction was stirred for 16hours. PS-Trisamine (3.75mmol/g, 133mg) was added , and stirring was continued for a further hour before filtration through a PTFE phase separating membrane. The product was purified by flash column chromatography (10g Silica), eluting 25% EtOAc in isohexane, and isolated as a white solid (118mg, 36%). NMR (DMSO-d_6): 1.40-1.70 (br s, 2H), 1.86 (d, 2H), 3.00-3.20 (br m, 2H), 3.71 (m, 1H), 4.0-4.3 (br d, 2H), 7.10 (d, 2H), 7.20 (t, 1H), 7.36 (t, 4H), 8.10 (m, 2H). M/z 391.47 $(M+MeCN+Na)^+$.

Examples 294-299 and Reference Examples 4 and 5

Using the procedure given for Example 293, the following Examples were synthesised substituting the phenyl chloroformate with the appropriate chloroformate reagent.



Ex	R	NMR
294	Me	(DMSO-d_6): 1.40 (qd, 2H), 1.76 (d, 2H), 2.97 (t, 2H), 3.58 (s, 3H), 3.59-3.68 (m, 1H), 3.98 (d, 2H), 7.34 (t, 2H), 8.02-8.15 (m, 2H)
RE 4	Et	(DMSO-d_6): 1.17 (t, 3H), 1.40 (qd, 2H), 1.76 (d, 2H), 2.96 (t, 2H), 3.54-3.70 (m, 1H), 3.91-4.10 (m, 4H), 7.34 (t, 2H), 8.00-8.12 (m, 2H)
295	Allyl	(DMSO-d_6): 1.42 (qd, 2H), 1.78 (d, 2H), 2.99 (t, 2H), 3.57-3.71 (m, 1H), 4.01 (d, 2H), 4.51 (d, 2H), 5.21 (dd, 2H), 5.84-6.00 (m, 1H), 7.34 (t, 2H), 8.00-8.13 (m, 2H)
296	$MeOCH_2CH_2$-	(DMSO-d_6): 1.41 (qd, 2H), 1.77 (d, 2H), 2.97 (t, 2H), 3.25 (s, 3H), 3.50 (t, 2H), 3.57-3.71 (m, 1H), 3.99 (d, 2H), 4.10 (t, 2H), 7.34 (t, 2H), 8.00-8.13 (m, 2H)
RE 5	Benzyl	(DMSO-d_6): 1.43 (qd, 2H), 1.78 (d, 2H), 3.01 (t, 2H), 3.56-3.72 (m, 1H), 4.03 (d, 2H), 5.07 (s, 2H), 7.24-7.46 (m, 7H), 8.01-8.15 (m, 2H)
297	Isopropyl	(DMSO-d_6): 1.17 (d, 6H), 1.39 (qd, 2H), 1.75 (d, 2H), 2.94 (t, 2H), 3.55-3.71 (m, 1H), 3.98 (d, 2H), 4.69-4.85 (m, 1H), 7.34 (t, 2H), 8.01-8.12 (m, 2H)
298	4-Fluorophenyl	(DMSO-d_6): 1.41-1.69 (br s, 2H), 1.85 (d, 2H), 2.95-3.25 (b m, 2H), 3.64-3.80 (m, 1H), 3.97-4.29 (br d, 2H), 7,11-7.25 (m, 4H), 7.36 (t, 2H), 8.03-8.17 (m, 2H)

Ex	R	NMR
299	4-Methoxyphenyl	(DMSO-d_6): 1.40-1.70 (br s, 2H), 1.84 (d, 2H), 2.90-3.25 (br s, 2H), 3.61-3.79 (m, 4H), 3.93-4.28 (br s, 2H), 6.89 (d, 2H), 7.03 (d, 2H), 7.36 (t, 2H), 8.01-8.17 (m, 2H)

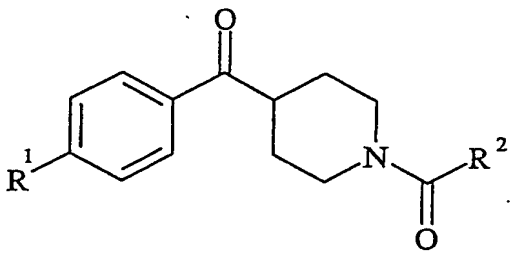
Example 300

1-(4-Fluoroanilinocarbonyl)-4-(4-fluorobenzoyl)piperidine

To a stirred solution of 4-(4-fluorobenzoyl)piperidine hydrochloride (200mg, 0.82mmol) and triethylamine (87mg, 0.86mmol) in DCM (4ml) was added 4-fluorophenyl isocyanate (101mg, 0.74mmol). The reaction was left to stir at room temperature for 15 minutes then worked up. Reaction transferred to a separating funnel and diluted to approximately 5ml with DCM. The DCM was washed with 1M HCl (10ml), water (10ml) and brine (5ml) then dried ($MgSO_4$), filtered and evaporated to yield a solid (153mg, 54%). NMR (DMSO-d_6): 1.50 (m, 2H), 1.80 (br d, 2H), 2.95 (t, 2H), 3.65 (m, 1H), 4.10 (br d, 2H), 7.05 (t, 2H), 7.35 (t, 2H), 7.45 (m, 2H), 8.10 (m, 2H), 8.50 (s, 1H); m/z 345.

Examples 301-312 and Reference Examples 6 and 7

The procedure described in Example 300 was repeated using the appropriate reagents to replace the "4-(4-fluorobenzoyl)piperidine hydrochloride" and "4-fluorophenyl isocyanate" to obtain the compounds described below.



Ex	R^1	R^2	NMR	M/z
301	6-Bromonaphth-2-ylsulphonyl	Me_2N-	1.25 (m, 2H), 1.73 (d, 2H), 2.70 (s, 6H), 2.80 (t, 2H), 3.53 (m, 3H), 7.82 (d, 1H), 7.97 (d, 1H), 8.15 (m, 6H), 8.36 (s, 1H), 8.78 (s, 1H)	531

Ex	R^1	R^2	NMR	M/z
302	6-Bromonaphth-2-ylsulphonyl	H_2N-	1.33 (m, 2H), 1.70 (d, 2H), 2.80 (t, 2H), 3.57 (m, 1H), 3.90 (d, 2H), 5.87 (s, 2H), 7.82 (d, 1H), 7.97 (d, 1H), 8.15 (m, 6H), 8.36 (s, 1H), 8.78 (s, 1H)	503
303	Cl	Me_2N-	1.40-1.58 (m, 2H), 1.70-1.80 (br d, 2H), 2.73 (s, 6H) 2.78-2.94 (br t, 2H), 3.50-3.63 (br d, 3H), 7.55-7.62 (d, 2H), 7.97-8.03 (d, 2H)	295.43
304	Fl	$(i\text{-Pr})_2N$-		355.53
305	Fl	Piperidin-1-yl		319.50
306	Cl	Anilino	1.40-1.62 (m, 2H), 1.73-1.90 (br d, 2H), 2.90-3.08 (app t, 2H), 3.58-3.75 (m, 1H), 4.06-4.24 (br d, 2H), 7.85-7.98 (pp t, 1H), 7.15-7.30 (app t, 2H), 7.38-7.53 (app d, 2H), 7.56-7.68 (app d, 2H), 7.96-8.10 (app d, 2H), 8.40-8.55	343.42
RE 6	Fl	Me_2N-	1.40-1.68 (m, 2H), 1.68-1.90 (br d, 2H), 2.58-3.0 (m, 8H), 3.50-3.75 (m, 3H), 7.28-7.50 (m, 2H), 8.0-8.22 (m, 2H)	279.46
RE 7	Fl	3-Chloroanilino		361.42
307	Fl	Benzylamino		341.8
308	Fl	Anilino		279.42
309	Fl	2-Fluoroanilino	1.41-1.62 (m, 2H), 1.74-1.90 (d, 2H), 2.93-3.10 (t, 2H), 3.59-3.75 (m, 1H), 4.03-4.20 (d, 2H), 7.0-7.23 (m, 3H), 7.30-7.50 (m, 3H), 8.0-8.15 (m, 2H), 8.17-8.30 (s, 1H)	345.45

Ex	R^1	R^2	NMR	M/z
310	Fl	3,4-Difluoroanilino		363.45
311	Fl	Morpholino	1.40-1.59 (m, 2H), 1.70-1.82 (br d, 2H), 3.84-2.97 (app br t, 2H), 3.03-3.17 (m, 4H), 3.50-3.70 (m, 7H), 7.27-7.40 (app t, 2H), 8.00-8.13 (m, 2H)	321.47
312	Fl	3-Methylanilino		341.47

Example 313

1-(4-Fluorobenzoyl)-4-(2-fluorobenzoyl)piperidine

Magnesium (55mg, 2.25mmol) was placed in a flask and covered with ether (6ml). The reaction was briefly stirred under Argon before the addition of a crystal of iodine. The reaction was cooled to 0°C before the slow addition of a solution of 2-fluroiodobezene (500mg, 2.25mmol) in ether (2ml). The reaction was then slowly warmed to 30°C but did not seem to exotherm. At this point 1-(4-fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl) piperidine (Method 2; 1g, 3.38mmol) was added and the reaction was left to stir for 3 hours. The reaction was then quenched with sat NH_4Cl (10ml) and extracted with EtOAc (2 x 10ml). The combined organic fractions were washed with brine (10ml) then dried ($MgSO_4$), filtered and evaporated to yield an oil. Oil purified by column chromatography (10% EtOAc/isohexane to 50% EtOAc/isohexane) to yield an oil. This oil was not clean so the material was further purified by prepLCMS (1-40% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN) to yield a solid (1mg, 0.14%). m/z 330.

Example 314

1-(4-Fluorobenzoyl)-4-(pyrid-2-ylcarbonyl)piperidine

Ethyl magnesium bromide (1M soln. in THF - 380µl, 0.38mmol) was added to a solution of 2-iodopyridine (70mg, 0.34mmol) in THF (4mls) at room temperature under an inert atmosphere. After stirring for 40 minutes, 1-(4-fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl) piperidine (Method 2; 120mg, 0.41mmol) was added as a solution in THF (1ml). After stirring at room temperature overnight, more Grignard reagent (1.36mmol – generated as before) was added. The reaction mixture was stirred for a further 64h before being quenched with saturated ammonium chloride solution (10ml). The mixture was

extracted with DCM (2x10ml) before drying ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (50% EtOAc/isohexane – 80% EtOAc/isohexane). Yield – 31mgs (29%). NMR: 0.95 (m, 2H), 1.77 (m, 2H), 2.00 (m, 2H), 3.14 (m, 2H), 4.17 (m, 1H), 7.08 (m, 2H), 7.45 (m, 3H), 7.85 (m, 1H), 8.06 (m, 1H), 8.68 (m, 1H); m/z 313.

Example 315

1-(4-Fluorobenzoyl)-4-(fur-2-ylcarbonyl)piperidine

n-Butyl lithium (1.6M in hexanes – 1.23ml, 1.97mmol) was added dropwise under an inert atmosphere to a solution of furan (120µl, 1.64mmol) in THF (8ml) at 0°C (ice bath). The reaction mixture was allowed to warm to room temperature and stirred for 20min before re-cooling to 0°C. Magnesium bromide (363mg, 1.97mmol) was added to the reaction mixture followed by 1-(4-fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl) piperidine (Method 2; 120mg, 0.41mmol) in THF (1ml). The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated ammonium chloride solution (20ml) and then extracted with EtOAc (2x20ml). The organic phase was further washed with water (20ml) before drying ($MgSO_4$) and solvent removal *in vacuo*. The resulting yellow gum was triturated with Et_2O/Isohexane to yield a yellow solid (60mg, 49%). NMR (DMSO-d_6): 1.52 (m, 2H), 1.77 (m, 2H), 3.07 (m, 2H), 3.43 (m, 1H), 6.72 (m, 1H), 7.25 (m, 2H), 7.45 (m, 2H), 7.55 (m, 1H), 7.98 (m, 1H); m/z 302.

Example 316

1-(Fur-2-ylcarbonyl)-4-(3-methoxybenzoyl)piperidine

To a stirred solution of 4-(3-methoxybenzoyl)piperidine (Method 3; 52mg, 0.24mmol) and triethylamine (26mg, 0.26mmol) in DCM (3ml) was added 2-furoyl chloride (28mg, 0.21mmol). The reaction was stirred at room temperature for 1 hour then worked up. The reaction was transferred to a separating funnel then diluted to ~10ml with DCM. The DCM was then washed with 1M HCl (5ml), sat $NaHCO_3$ (5ml) and brine (5ml) then dried $MgSO_4$, filtered and evaporated to yield a solid (18mg, 24%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 3.25 (t, 2H), 3.75 (m, 1H), 3.90 (s, 3H), 4.30 (d, 2H), 6.60 (m, 1H), 6.90 (m, 1H), 7.20 (m, 1H), 7.50 (m, 2H), 7.60 (d, 1H), 7.75 (s, 1H); m/z 314.

Preparation of Starting Materials

The starting materials for the examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

Method 1

1-(4-Fluorobenzoyl)-4-(ethoxycarbonyl)piperidine

To a stirred solution of ethylisonipecotate (2.5g, 0.016mol) and triethylamine (1.77g, 0.017mol) in DCM (100ml) was added 4-flurobenzoyl chloride (2.39g, 0.015mol). The reaction was stirred at room temperature for one hour then worked up. The reaction was transferred to a separating funnel and diluted to ~150ml with DCM. The DCM was washed with 1M HCl (100ml), sat $NaHCO_3$ (100ml)and brine (50ml) then dried ($MgSO_4$), filtered and evaporated to yield an oil (3.67g, 83%). NMR (DMSO-d_6): 1.20 (t, 3H), 1.60 (m, 2H), 1.90 (m, 2H), 2.65 (m, 1H), 3.10 (m, 2H), 3.95 (br d, 2H), 4.10 (q, 2H), 7.25 (t, 2H), 7.55 (m, 2H); m/z 280.

Method 2

1-(4-Fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine

To a stirred solution of 1-(4-fluorobenzoyl)-4-(ethoxycarbonyl)piperidine (Method 1; 1g, 3.58mmol) in anhydrous THF (30ml) was added N,O-dimethylhydroxylamine hydrochloride (350mg, 3.58mmol). The resulting solution was cooled to –10°C before the addition of a 2M solution of isopropyl magnesium chloride (3.58ml, 7.16mmol). The reaction was stirred at –10°C for 15 minutes then allowed to warm to room temperature. The reaction was stirred at room temperature for 60 minutes before the addition of further isopropyl magnesium chloride (0.18ml, 0.36mmol). The reaction was then stirred for a further 10 minutes before working up. The reaction was quenched with sat NH_4Cl solution (~20ml) then extracted with EtOAc (2 x 20ml). The combined organic layers were washed with brine then dried ($MgSO_4$), filtered and evaporated to yield the title compound (880mg, 84%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.80 (m, 2H), 3.00 (m, 1H), 3.10 (m, 2H), 3.15 (s, 3H), 3.70 (s, 3H), 4.05 (m, 2H), 7.20 (t, 2H), 7.45 (m, 2H); m/z 295.

Method 3

4-(3-Methoxybenzoyl)piperidine

To a stirred 1M solution of 3-methoxyphenyl magnesium bromide in THF (12ml, 0.012mols) was added a solution of 1-acetylpiperidine-4-carbonitrile (1g, 6.57mols) in THF (4ml). The reaction was then left to stir overnight in the dark. The reaction was quenched with sat NH_4Cl and then warmed to 40°C and stirred at this temperature for 1 hour. The volatile organics were removed under reduced pressure and the resulting aqueous layer was extracted with ether (2 x 20ml). The organic layers were combined, washed with brine then evaporated to yield an oil. This oil was dissolved in dioxane (7ml) and treated with 5M HCl (7ml). The reaction was heated to 100° and stirred at this temperature overnight. The reaction was the cooled to room temperature and evaporated under reduced pressure. The resulting crude material was dissolved in DCM and washed with 2M NaOH, water and brine. The solvent was evaporated under reduced pressure to yield a yellow oil. This oil was dissolved in a small amount of MeOH and loaded onto an SCX-2 column. The column was eluted with MeOH until no further impurities eluted off. The desired product was then eluted with 1% NH_3/MeOH to yield an oil (52mg, 4%). m/z 220.

Method 4

3-Methyl-4-(4-fluorobenzoyl)piperidine hydrochloride

To a stirred solution of 1-(t-butoxycarbonyl)-3-methyl-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine (Method 5; 85mg, 0.3mmol) in anhydrous THF (2ml) at 0°C was added a 1M solution of 4-fluorophenyl magnesium bromide in THF (1ml, 1mmol). The reaction was stirred at 0°C for 1 hour then allowed to warm to room temperature and stirred for a further 90 minutes. At this stage further 4-fluorophenyl magnesium bromide (0.5ml, 0.5mmol) was added and the reaction was stirred for a further hour. The reaction was quenched with sat NH_4Cl solution (~5ml) then extracted with EtOAc (2 x 5ml). The combined organic layers were then washed with brine (~5ml), dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was dissolved in DCM (~1ml) and treated with TFA (~0.1ml) then left to stir overnight at room temperature. The reaction mixture was then transferred to a separating funnel and diluted to ~5ml with DCM. The DCM layer was then washed with 1M NaOH and evaporated to yield an oil. This oil was eluted through an Isolute SCX-2 column using MeOH. When all impurities had eluted off the product was eluted with 1% NH_3/MeOH. This product was dissolved in ether then treated with 1.1eq of 1M HCl in

ether. The resulting suspension was evaporated under reduced pressure to yield a solid. This solid was left under high vac overnight to yield the product as the hydrochloride salt (22mg, 30%). NMR (DMSO-d_6): 0.90 (d, 3H), 1.90 (m, 1H), 2.00 (m, 2H), 2.40 (m, 1H), 3.20 (m, 3H), 3.90 (m, 1H), 7.30 (t, 2H), 8.05 (m, 2H), 8.60 (br s, 2H); m/z 222.

Method 5

1-(*t*-Butoxycarbonyl)-3-methyl-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine

To a stirred solution of N-Boc-3-methyl-4-piperidine carboxylic acid (100mg, 0.41mmol), N,O-dimethyl hydroxylamine hydrochloride (40mg, 0.41mmol) and N-methyl morpholine (41mg, 0.41mmol) in DCM (5ml) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (79mg, 0.41mmol). The resulting solution was stirred at room temperature for 48 hours. The reaction mixture was transferred to a separating funnel and washed with 1M HCl (2 x 5ml), sat $NaHCO_3$ (5ml) and brine (5ml) then dried ($MgSO_4$), filtered and evaporated to yield a solid (85mg, 73%). NMR (DMSO-d_6): 0.85 (d, 3H), 1.45 (s, 9H), 1.47 (m, 1H), 1.80 (m, 1H), 2.10 (m, 1H), 3.05 (m, 3H), 3.10 (s, 3H), 3.20 (m, 1H), 3.65 (m, 1H), 3.70 (s, 3H), 3.80 (m, 1H).

Method 6

1-(4-Fluorophenylsulphonyl)-4-(ethoxycarbonyl)piperidine

To a stirred solution of ethylisonipecotate (15g, 0.095mol) and triethylamine (10.6g, 0.105mol) in DCM (380ml) at 0°C was added a solution of 4-fluorobenzenesulfonylchloride (17.6g, 0.09mol) in DCM (20ml). The reaction was stirred at 0°C for 10 minutes then allowed to warm to room temperature and stirred for a further 2 hours. The reaction mixture was transferred to a separating funnel and washed with 2M HCl (80ml), water (40ml), sat $NaHCO_3$ (40ml) and brine (40ml) and then dried ($MgSO_4$), filtered and evaporated to yield a white solid (25.75g, 88%). NMR (DMSO-d_6): 1.15 (t, 3H), 1.55 (m, 2H), 1.85 (m, 2H), 2.35 (m, 1H), 2.45 (m, 2H), 3.50 (m, 2H), 4.05 (q, 2H), 7.45 (t, 2H), 7.80 (m, 2H); m/z 316.

Method 7

1-(Isopropylsulphonyl)-4-(ethoxycarbonyl)piperidine

The title compound was prepared by the procedure of Method 6. NMR (DMSO-d_6): 1.20 (m, 9H), 1.50 (m, 2H), 1.85 (m, 2H), 2.55 (m, 1H), 2.85 (m, 2H), 3.30 (m, 1H), 3.60 (m, 2H), 4.10 (q, 2H); m/z 264.

Method 8

1-(4-Fluorophenylsulphonyl)-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine

To a stirred solution of 1-(4-fluorophenylsulphonyl)-4-(ethoxycarbonyl)piperidine Method 6; 8g, 0.025mol) and N,O-dimethyl hydroxylamine hydrochloride (2.49g, 0.025mol) in anhydrous THF (200ml) at 0°C was added a 2M solution of iso propyl magnesium chloride in THF (26ml, 0.053mol). The reaction was stirred at 0°C for ten minutes then allowed to warm to room temperature and left to stir for two and a half hours. The reaction was quenched with sat NH_4Cl solution (100ml) and extracted with EtOAc (2x100ml). The combined organic phases were washed with brine then dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (50g Silica, 20% EtOAc/isohexane to 60% EtOAc/isohexane) to yield an oil which crystallised on standing (6g, 73%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.80 (m, 2H), 2.55 (m, 2H), 2.70 (m, 1H), 3.05 (s, 3H), 3.65 (m, 5H), 7.40 (t, 2H), 7.80 (m, 2H); m/z 331.

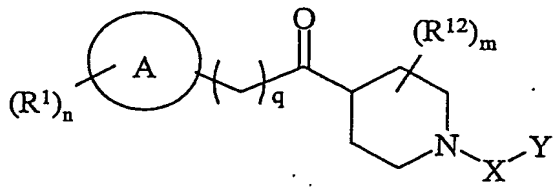
Method 9

1-(Isopropylsulphonyl)-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine

The title compound was prepared by the procedure of Method 8, except the product did not require chromatography. NMR (DMSO-d_6): 1.20 (d, 6H), 1.50 (m, 2H), 1.75 (m, 2H), 2.85 (m, 1H), 2.95 (m, 2H), 3.10 (s, 3H), 3.30 (m, 1H), 3.70 (s, 3H); m/z 279.

Claims

1. The use of a compound of formula (I):



(I)

wherein:

Ring A is selected from carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^1 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-5; wherein the values of R^1 may be the same or different;

X is a direct bond, -C(O)-, -S(O)$_2$-, -C(O)NR^{11}-, -C(S)NR^{11}-, -C(O)O- or -CH$_2$-; wherein **R^{11}** is selected from hydrogen and C_{1-4}alkyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl,

N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

R^3 and **R^6** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

R^4, **R^5**, **R^7** and **R^9** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;

R^{12} is methyl or ethyl;

m is 0 or 1;

q is 0 or 1;

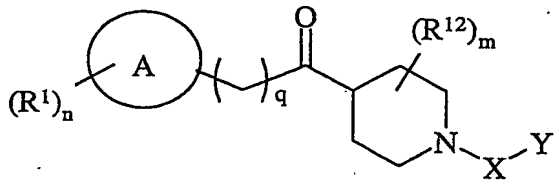
or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

ABSTRACT

TITLE :CHEMICAL COMPOUNDS

The use of a compound of formula (I):



(I)

in the manufacture of a medicament for use in the inhibition of 11βHSD1 is described.